

# Intramolecular 1,3-dipolar cycloaddition of unsaturated nitrones derived from methyl $\alpha$ -D-glucopyranoside

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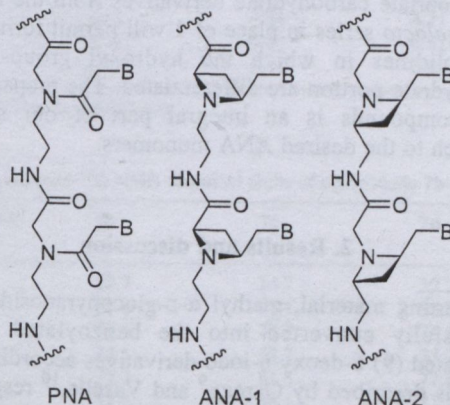
**Abstract**—The intramolecular 1,3-dipolar cycloaddition of unsaturated nitrones derived from methyl  $\alpha$ -D-glucopyranoside with 2-furaldehyde has been studied. This cycloaddition was found to afford three 9-oxa-1-azabicyclo[4.2.1]nonane diastereomers in a 3:1:1 ratio [with the principal isomer possessing a (3*S*,4*R*,5*S*,6*S*,8*S*) configuration, determined by NMR spectroscopy]. The effects of different Lewis acid catalysts (MgCl<sub>2</sub>, ZnCl<sub>2</sub> and BF<sub>3</sub>·OEt<sub>2</sub>) on yields and diastereomeric ratios have been examined in detail. The best result (90% yield) was achieved when MgCl<sub>2</sub> was present (in toluene, 120 °C bath temperature, 12 h). The stereoselectivity of the 1,3-dipolar cycloaddition was not significantly altered under the conditions investigated.

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## 1. Introduction

Peptide nucleic acids (PNAs) are nucleic acid mimics bearing a pseudopeptide backbone (Fig. 1).<sup>1,2</sup> They possess very favourable hybridisation properties with nucleic acid targets, display high chemical and biological stabilities and have the potential to be used as both antisense and antigene therapeutic agents. Unfortunately, PNA has low lipid penetration and, consequently, poor cellular uptake. In an attempt to overcome these undesirable attributes, we have designed a conformationally restricted oligonucleotide analogue whose backbone should be positively charged under physiological conditions. These new chiral nucleoside analogues are termed azetidine nucleic acids (ANAs, Fig. 1). The pivotal step in the synthesis of the ANA monomers, needed for construction of the oligomers, is a diastereoselective intramolecular 1,3-dipolar cycloaddition involving unsaturated nitrones derived from carbohydrate precursors. Subsequent transformations on the corresponding isoxazolidines obtained should then afford the desired azetidine derivatives (Fig. 2).

We envisage that it will be possible to control the stereochemical outcome of the intramolecular 1,3-dipolar cycloaddition by virtue of steric constraint so that the actual number of isoxazolidine isomers produced would be reduced compared to the theoretical. The use of different Lewis acid catalysts is anticipated to improve both the stereoselectivity and reactivity of the nitrone. The mechanism of such 1,3-dipolar cycloadditions has been extensively studied by several authors.<sup>3</sup> Nitrones are nucleophiles which



**Figure 1.** The structure of PNA and ANA oligomers (B, nucleobase). Only one diastereoisomer is shown for each ANA structure.

**Keywords:** 1,3-Dipolar cycloaddition; Isoxazolidines; Bicyclic 1,2-oxazepanes; 9-Oxa-1-azabicyclo[4.2.1]nonanes; Asymmetric synthesis.

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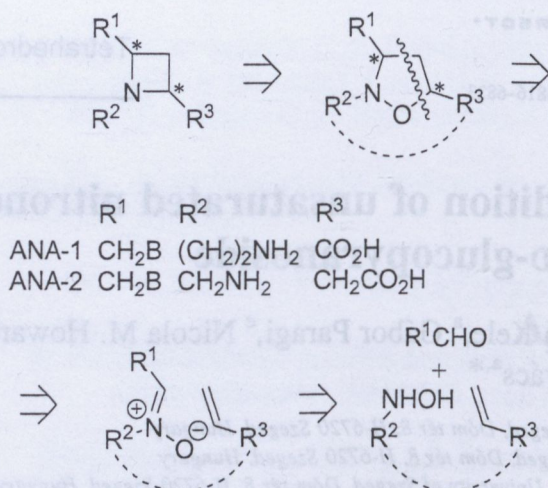


Figure 2. Retrosynthetic analysis of ANA monomers.

co-ordinate strongly to Lewis acids to form nitron/Lewis acid complexes. These complexes are generated easily and they serve to assist in 1,3-dipolar cycloadditions through stabilization of the corresponding transition state and decreasing the energy gap between the LUMO and HOMO of one of the substrates.<sup>4,5</sup> Thus, a series of catalysts (metals and their complexes) has been developed for use in either normal or inverse electron demand 1,3-dipolar cycloadditions, for example, Mg<sup>2+</sup>, Ti<sup>2+</sup>, Zn<sup>2+</sup>, Ni<sup>2+</sup>, Pd<sup>2+</sup>, Yb<sup>3+</sup>, B(III), Al<sup>3+</sup>, Cu<sup>2+</sup>.<sup>3</sup> The 1,3-dipolar cycloaddition of nitrones bearing heteroaryl rings with electron-deficient alkenes has been investigated in detail by Merino et al.<sup>6–8</sup>

Our interest in the development of an efficient route for the synthesis of chiral isoxazolidines and, ultimately, azetidines led us to therefore consider using a similar strategy, utilizing unsaturated nitrones derived from carbohydrates, for their preparation. The starting material employed for the work reported herein was methyl  $\alpha$ -D-glucopyranoside (**1**) (Fig. 3). In this case, the 1,3-dipolar cycloaddition investigated was a model reaction in order that suitable reaction procedures for performing such cycloadditions could be identified. It is envisaged that future employment of appropriate carbohydrate derivatives from the D-manno and D-galacto series in place of **1** will permit formation of isoxazolidines in which the hydroxyl groups in the carbohydrate portion are differentiated. The preparation of such compounds is an integral part of our synthetic approach to the desired ANA monomers.

## 2. Results and discussion

The starting material, methyl  $\alpha$ -D-glucopyranoside **1**, was successfully converted into the benzoylated (**2**) and benzylated (**9**) 6-deoxy-6-iodo derivatives according to the methods described by Garegg<sup>9</sup> and Vasella,<sup>10</sup> respectively (Fig. 3). The subsequent Boord reaction on the halo derivatives [**2**→**3**, **9**→**10** (Fig. 3)] was accomplished upon treatment with zinc followed by sonication.<sup>11</sup> However, it was discovered that acceptable yields of the products **3** and **10** were only obtained for small scale

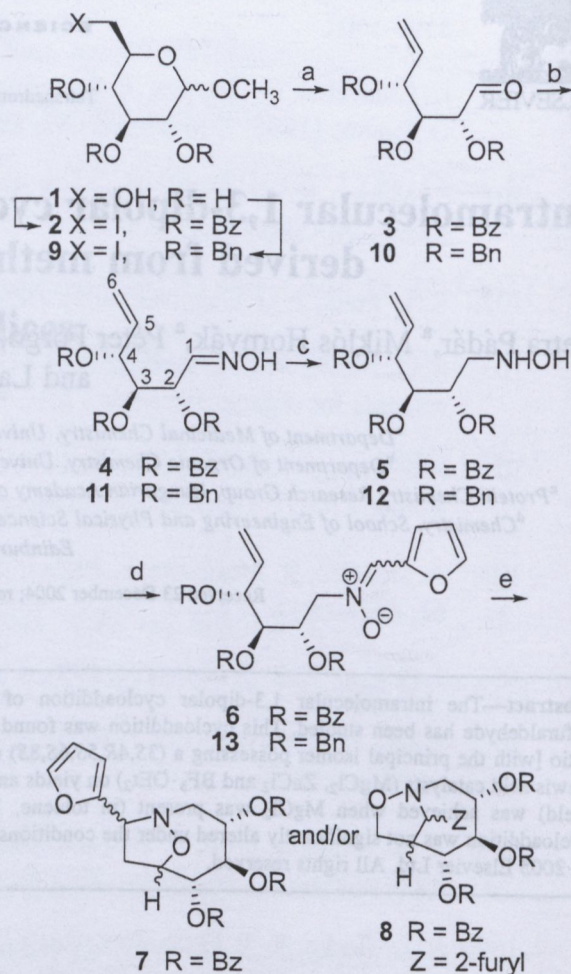


Figure 3. a: (**2**→**3**, **9**→**10**): Zn, sonication (1.6 g scale: 90%, 5 g scale: 30%) or Zn and Co(II)phthalocyanine (5 g scale: 70%), b: NH<sub>2</sub>OH·HCl, NaHCO<sub>3</sub> (70%), c: NaBH<sub>3</sub>CN, HCl/dioxane, d: 2-furaldehyde, toluene (c + d: 30–40%), 4 Å MS, 50 °C, 18 h, e: toluene, 120 °C, 4 Å MS, Lewis acid catalyst, 7: 9-oxa-1-azabicyclo-[4.2.1]nonane, 8: 8-oxa-1-azabicyclo-[4.2.1]nonane skeletons.

reactions (up to 1.6 g of **2** or **9** afforded **3** or **10** in ca. 90% yields). Thus, several attempts were made to increase the scale of this reaction by employing activated zinc instead. This was prepared according to established methods,<sup>13</sup> for example, zinc–copper alloy<sup>14</sup> or the reduction of anhydrous zinc chloride with various alkali metals in the presence of naphthalene.<sup>15,16</sup> Heating solutions of **2** or **9** in ethanol at reflux in the presence of activated zinc produced by either method, afforded the same result, with respect to scale and yield (1 g scale ca. 70%, 5 g scale ca. 30% yield). When more than 5 g of the starting 6-deoxy-6-iodo derivative (**2** or **9**, respectively) was used and the activated zinc was prepared in situ from zinc chloride and lithium, the reaction also failed to go to completion. In this case, though, the remaining lithium in the reaction mixture caused decomposition of the unsaturated aldehyde and, also, prevented addition of water to the reaction mixture, which is necessary to dissolve zinc salts from the surface of zinc. Thus, all these procedures gave optimum product yields up to a maximum 1 g scale. Upon conducting further investigations into this Boord reaction, we found that, for large scale reactions, reasonable yields of the products **3** and **10** could be obtained



when zinc and cobalt(II) phthalocyanine was utilised (Kleban et al.<sup>12</sup> employed zinc and vitamin B<sub>12</sub> for the same purpose) rather than zinc and sonication (5 g scale, ca. 70% yield).

Having prepared unsaturated aldehydes **3** and **10**, the next step in our synthetic pathway involved treatment with hydroxylamine at room temperature<sup>17</sup> to give oximes **4** and **11**, respectively (*E/Z* isomers in 1:1 ratio) (Fig. 3). Subsequently, **4** or **11**<sup>18</sup> were reduced with sodium cyanoborohydride and HCl/1,4-dioxane at the appropriate pH, depending on the protecting groups present, to afford **5** or **12**, respectively (Fig. 3). These hydroxylamines were used in the next step without further purification in order to avoid their decomposition. The mixture of HCl/1,4-dioxane had to be added slowly due to the acid sensitive nature of the benzoyl protecting groups and because further reduction of the hydroxylamine could easily occur at low pH which would result in formation of the amine instead. It was envisaged that this amine by-product would hinder the subsequent condensation step as it could react with 2-furaldehyde to give a Schiff's base, drastically reducing the yield of the cycloaddition reaction. Therefore, in an attempt to overcome this limitation, we have investigated performing the reduction of **4** and **11** in phosphate buffer solutions at various pHs, ranging from 4 to 8. Unfortunately, to date, all attempts have proved unsuccessful and so our original approach for preparing hydroxylamines **5** and **12** has been retained for the present work. Finally, crude hydroxylamines **5** and **12** were condensed with 2-furaldehyde to furnish the desired nitrones, **6** and **13**, required for investigation of the 1,3-dipolar intramolecular cycloaddition reaction (Fig. 3). These were afforded in overall yields of 30–40% for the two steps, after purification.

With nitrones **6** and **13** to hand, it was now possible to investigate the intramolecular 1,3-dipolar cycloaddition. This was simply accomplished by heating a solution of the appropriate nitrone in toluene at reflux in the presence of 4 Å molecular sieves (Fig. 3). Unfortunately, for the benzyl protected nitrone **13**, this reaction proved to be sluggish (toluene, reflux, 1 week) and very low yielding (<10%); therefore it was abandoned. For the benzoyl nitrone **6**, this reaction was found to be more successful and gave isoxazolidine **7** (Fig. 3) as a mixture of diastereoisomers in 17–90% yield as expected. These isomers were subsequently separated by column chromatography and characterised by NMR spectroscopy as the 9-oxa-1-azabicyclo[4.2.1]nonane diastereoisomers **7b–7d** (Fig. 4).

We were unable to isolate the fourth diastereoisomer from the 9-oxa series (**7a**) (Fig. 4) as its yield was negligible. We assume that the other alternative product from this cycloaddition, 8-oxa-1-azabicyclo[4.2.1]nonane **8** (Fig. 3), did not form because of steric hindrance between the furyl side chain and the oxazepane ring.

Tables 1 and 2 show selected proton and carbon chemical shifts recorded in the <sup>1</sup>H and <sup>13</sup>C NMR spectra of compounds **7b–7d**. Upon assignment of the individual resonances by means of <sup>1</sup>H, <sup>13</sup>C, HSQC and HMBC NMR measurements, it was shown that protons H-6 and H-8 adopt a relative *trans* arrangement in the principal isomer **7b**

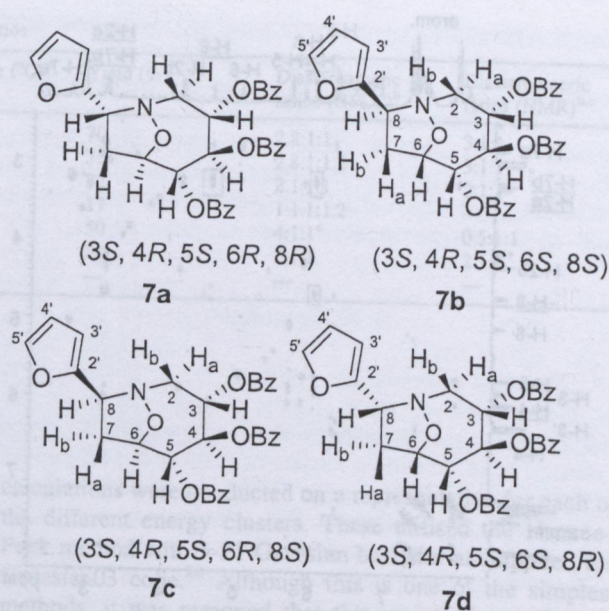


Figure 4. The structures of 9-oxa-1-azabicyclo[4.2.1]nonanes **7a–7d**.

whereas the equivalent protons in isomers **7c** and **7d** assume a *cis* arrangement. The NOESY spectrum of **7b** (Fig. 5) indicates the spatial proximity of protons H-2a, H-4, and H-8 and that of H-7b, H-4, H-8. Protons H-7b and H-2a reside on the bottom face of the structure relative to the oxazepane ring. In addition, it appears that proton H-7b is located far from its neighbours, H-2a, H-4 and H-8, as no coupling between H-7b and H-2a was detected (Table 4).

Table 1. Selected <sup>1</sup>H NMR chemical shifts of compounds **7b–7d**

Compound/ atom	<b>7b</b>	<b>7c</b>	<b>7d</b>
H-2a (dd) <sup>a</sup>	3.22	3.60	3.02
H-2b (dd)	4.22	2.89	3.53
H-3	5.85 (m)	5.96 (ddd)	5.89 (ddd)
H-4 (dd)	6.00	6.21	5.98
H-5	5.68 (dd)	5.51 (d)	5.69 (dd)
H-6	5.02 (m)	4.82 (dd)	4.96 (ddd)
H-7a (ddd)	2.75	2.83	2.67
H-7b (ddd)	3.18	3.14	2.86
H-8 (dd)	4.63	4.74	4.71
H-3' (d)	6.28	6.60	6.51
H-4' (dd)	6.32	6.44	6.42

<sup>a</sup> Multiplicities in parenthesis.

Table 2. Selected <sup>13</sup>C NMR chemical shifts of compounds **7b–7d**

Compound/ atom	<b>7b</b>	<b>7c</b>	<b>7d</b>
C-2	58.7	54.7	52.2
C-3	68.8	68.1	66.8
C-4	73.1	74.7	74.6
C-5	73.1	79.2	73.2
C-6	77.7	81.8	77.6
C-7	34.2	38.1	31.2
C-8	65.4	60.9	64.1
C-2'	154.3	147.1	148.1
C-3'	106.2	111.2	111.1
C-4'	110.3	110.8	110.7
C-5'	142.3	143.6	143.4



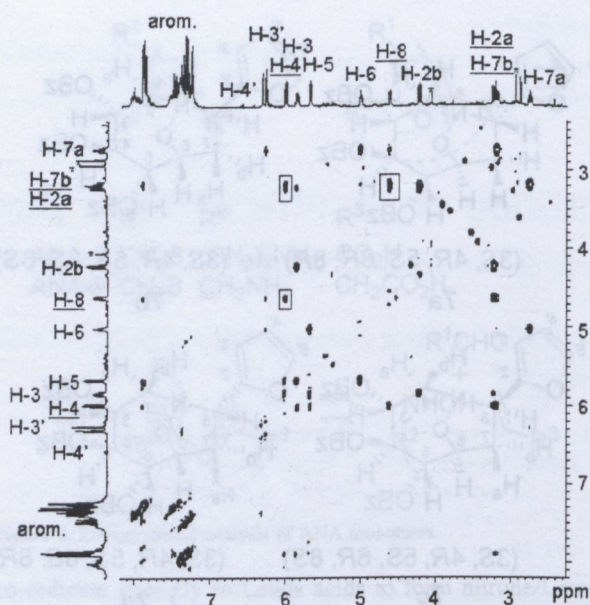


Figure 5. NOESY spectrum of compound **7b**. Crucial correlations between underlined protons are shown in boxes.

Table 3. Coupling constants for compounds **7b–7d** (Hz)

Compd/coupling constant	<b>7b</b>	<b>7c</b>	<b>7d</b>
$J_{2a,2b}$	13.8	15.0	12.5
$J_{2a,3}$	7.9	10.9	10.3
$J_{2b,3}$	4.9	4.0	4.0
$J_{3,4}$	9.2	10.9	10.1
$J_{4,5}$	7.9	7.6	8.7
$J_{5,6}$	6.0	—	5.8
$J_{6,7a}$	8.8	6.1	8.7
$J_{6,7b}$	3.8	10.0	6.2
$J_{7a,7b}$	13.1	13.5	13.2
$J_{7a,8}$	3.6	11.0	7.2
$J_{7b,8}$	8.5	9.5	11.2
$J_{3',4'}$	3.2	3.2	3.1
$J_{4',5'}$	1.9	2.0	1.9

Table 4 reveals that compounds **7b** and **7d** adopt similar structures. Naturally, though, the position of protons H-8 and H-3' in the furyl ring are reversed for isomer **7d** compared to isomer **7b** [**7b**: (8*S*), **7d**: (8*R*)]. This was confirmed by the coupling constants measured between protons H-6, H-7 and H-8 (Table 3). The only real difference between their structures is that proton H-7b is located closer to protons H-2a and H-4 in isomer **7d** (evaluated from the dihedral angles). Thus, for isomer **7d**, a cross-correlation peak was visible in the NOESY spectrum (H-7b/H-2a/H-4). In the case of isomer **7c**, protons H-3'/H-3/H-7a and H-5/H-3/H-7a on the top face of the oxazepane ring are found to be in close proximity to each other, according to the

NOESY spectrum recorded. By taking into account the coupling constants for all the isoxazolidine and 1,2-oxazepane ring protons in all three isomers, we have been able to determine the configuration of each of the newly formed chiral centres [**7b**: (6*S*,8*S*); **7c**: (6*R*,8*S*); and **7d**: (6*S*,8*R*) (Fig. 4)]. The stereochemistry of the remaining chiral centres have been deduced from D-glucose and the conformation of the 1,2-oxazepane ring.

The effects of different Lewis acid catalysts ( $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{ZnCl}_2$ ,  $\text{MgCl}_2$ ), solvents, absence or presence of 4 Å molecular sieves and reflux time on yields and diastereomeric ratios for this intramolecular 1,3-dipolar cycloaddition with nitron **6** (Fig. 3) have been examined in detail (Table 5). The diastereomeric ratios of **7b–7d** obtained from each reaction were initially determined by the combined use of TLC and RP-HPLC. However, as this method proved cumbersome and inaccurate, alternatives were sought. The fortunate finding that, in the  $^1\text{H}$  NMR spectra, the peaks assigned to protons H-3' and H-4' of the furyl ring were located in unique positions for each of the three isomers, that is, **7b–7d**, led us to investigate using  $^1\text{H}$  NMR spectroscopy instead for these measurements. This afforded ratios which were in good agreement with those obtained previously from RP-HPLC experiments and so, due to its convenience and accuracy, it became the method of choice.

From Table 5, it can be seen that when the intramolecular 1,3-dipolar cycloaddition was performed in toluene, the reflux time (24 or 48 h) had no effect on yield or diastereomeric ratio. However, since nitron **6** decomposed quickly at temperatures above 100 °C, even under an argon atmosphere, it was not advantageous to heat the reaction in toluene at reflux for more than 24 h. 1,4-Dioxane was found to be an unsuitable solvent for this reaction; the mixture of isomers **7b–7d** was afforded in only 17% yield.

We have established that the main diastereoisomer obtained from these cycloaddition reactions (except when 1,4-dioxane and  $\text{ZnCl}_2$  was used) was **7b**, bearing the (6*S*,8*S*) configuration at the newly formed chiral centres (Table 5). The maximum yield for this intramolecular 1,3-dipolar cycloaddition was achieved when  $\text{MgCl}_2$  was added [90%, toluene, 120 °C (bath temperature), 12 h, Table 5]. Unexpectedly, in the presence of the harder Lewis acid catalyst,  $\text{BF}_3 \cdot \text{OEt}_2$ , most of the starting nitron **6** decomposed after only a few hours to give an undesired product which contained one less benzoyl group (as determined from MS data). As a result of this finding, we propose that this also attributed to the reduced yield observed for the reaction performed in the presence of  $\text{ZnCl}_2$ , although here decomposition of the nitron was slower.

In conclusion, we have ascertained that the optimum conditions for performing this 1,3-dipolar cycloaddition

Table 4. NOESY data of compounds **7b–7d**

Compd	Connected protons (upside positions) <sup>a</sup>	Connected protons (downside positions) <sup>a</sup>	Connected protons (peripheral positions) <sup>a</sup>
<b>7b</b>	H-3...H-2b; H-5...H-6	H-7b...H-8...H-4; H-8...H-2a...H-4	H-6...H-7a; H-7a...H-3'
<b>7c</b>	H-3'...H-3...H-7a H-3...H-5...H-7a H-3...H-2b	H-2a...H-4	H-7b...H-8; H-7b...H-6
<b>7d</b>	H-3...H-2b; H-5...H-6	H-7b...H-2a...H-4...H-3'	H-7a...H-6; H-7a...H-8

<sup>a</sup> Relative to the 9-oxa-1-azabicyclo[4.2.1]nonane skeleton as shown in Figure 6.



**Table 5.** The effect of Lewis acids and solvents on yields and diastereomeric ratios

Solvent, mol sieves	Catalyst	Time (h)	Temperature (°C) <sup>a</sup>	Yield (%)	Diastereomeric ratios (HPLC) <sup>b</sup>	Diastereomeric ratios (NMR) <sup>b,c</sup>
Toluene, 4 Å	—	24	120	70	2.8:1:1	3:1:1
Toluene	—	48	120	75	2.8:1:1.2	3:1:1
Benzene, 4 Å	—	24	80	32	2.1:1:1	2:1:1
1,4-Dioxane, 4 Å	—	24	100	17	1:1.1:1.2	— <sup>d</sup>
Toluene, 4 Å	ZnCl <sub>2</sub>	24	120	50	4:1:1 <sup>e</sup>	0.5:1:1
Toluene, 4 Å	MgCl <sub>2</sub>	12	120	90	2:1:1	2:1:1
Toluene, 4 Å	BF <sub>3</sub> ·OEt <sub>2</sub>	24	120	— <sup>f</sup>	—	—

<sup>a</sup> Bath temperature.  
<sup>b</sup> Ratio of isomers **7b**:**7c**:**7d** isolated from the reaction mixture.  
<sup>c</sup> Determined from the integral of protons H-3' and H-4'.  
<sup>d</sup> Not determined due to the presence of impurities.  
<sup>e</sup> Diastereomer **7b** could not be separated from an impurity.  
<sup>f</sup> The starting material decomposed and a by-product was formed (see text).

reaction with nitrone **6** (Fig. 3) involve using toluene as the solvent and MgCl<sub>2</sub> as the Lewis acid catalyst. It appears that if the Lewis acid catalyst added is hard, a side reaction involving elimination of a benzoyl protecting group from the starting nitrone becomes significant and this may be accompanied by decomposition and conversion of the furyl group, too. The stereoselectivity of the cycloaddition was found not to alter much under the conditions investigated here.

### 3. Theoretical investigations

In order to analyse the geometry of all four diastereoisomers of the isoxazolidine derivative (i.e., **7a–7d** (Fig. 4)) produced from the intramolecular 1,3-dipolar cycloaddition with nitrone **6** (Fig. 3), we have conducted a systematic computational investigation. This involved performing molecular dynamics simulations followed by high-level ab initio calculations. For the molecular dynamics studies, the ‘simulated annealing’ protocol described in the SYBYL program package<sup>19</sup> was employed to obtain the required starting geometries for isomers **7a–7d** for the subsequent higher level investigations. The Merck’s force field parameter set (MMFF94) was applied with its own charge distribution. The molecules were equilibrated for 2000 fs at 1200 K and then cooled to 50 K exponentially over 10,000 fs. In this way, 1000 conformations were provided for each isomer. Next a semi-empirical optimization using the PM3 method was performed and the results analysed were grouped according to their energies. Finally, ab initio

calculations were conducted on a representative for each of the different energy clusters. These utilised the Hartree–Fock method with 3-21 Gaussian basis set and applied the Gaussian03 code.<sup>20</sup> Although this is one of the simplest methods, it was reasoned that this was sufficient for our purposes. The conformations of the oxazepane rings for isomers **7b–7d** derived from the computational studies were found to be in very good agreement with the structures obtained previously from NMR studies. In Figure 6, the optimized geometry of isomer **7b** is presented. The spatial proximity of protons H-7b, H-8, H-4 and H-2a on the bottom face can be clearly seen. In addition to the theoretical calculations providing information about the geometry of isomers **7a–7d**, we had hoped that they could also be used to predict the diastereomeric ratio afforded by the cycloaddition reaction (**7a**:**7b**:**7c**:**7d** ≈ 0:3:1:1) based on the total energy of each of the isomers.

However, it appeared that, at this level of theory, significant differences could not be observed with the total energies for diastereoisomers **7a–7d** being approximately the same. In Table 6, the HF/3-21G total energies of the minimized geometries for each of the different isoxazolidine isomers are presented.

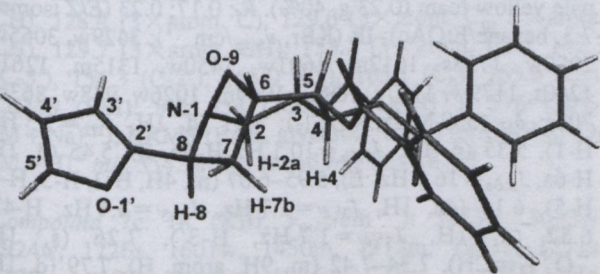
**Table 6.** Calculated total energies of compounds **7a–7d**<sup>a</sup>

Compound	Total energy (hartree)
<b>7a</b>	–1870.388634
<b>7b</b>	–1870.389014
<b>7c</b>	–1870.389014
<b>7d</b>	–1870.389272

<sup>a</sup> Ab initio (HF/3-21G method).

### 4. Conclusion

We have successfully synthesized a variety of isoxazolidine derivatives of chiral moieties employing a Lewis acid-catalyzed 1,3-dipolar cycloaddition. In our preliminary studies, the exclusive formation of 9-oxa-1-azabicyclo-[4.2.1]nonane diastereomers **7b–7d** (Fig. 4) from nitrone **6** (Fig. 3) has been observed. The maximum yield for the 1,3-dipolar cycloaddition reaction was achieved with MgCl<sub>2</sub> as the Lewis acid catalyst [toluene, 120 °C (bath temperature), 12 h]. The ratio of the diastereoisomers of **7b–7d** was 3:1:1 and this did not alter significantly under the different



**Figure 6.** The lowest-energy conformation of compound **7b** calculated by HF/3-21 method. Proximal hydrogen atoms of 9-oxa-1-azabicyclo[4.2.1]-nonane skeleton, supporting the configuration and conformation of the above compound (NMR evidence), are shown with the H prefix. Carbon atoms of the above skeleton and those of the furan skeleton (primed numbers) are labelled without the C prefix for clarity.



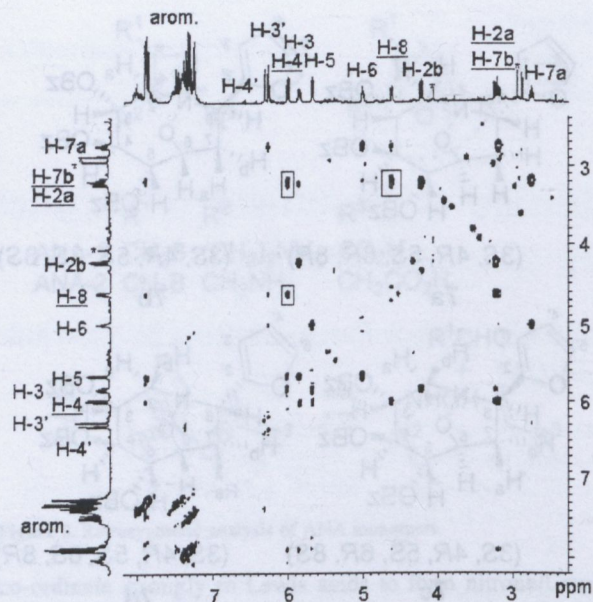


Figure 5. NOESY spectrum of compound **7b**. Crucial correlations between underlined protons are shown in boxes.

Table 3. Coupling constants for compounds **7b–7d** (Hz)

Compd/coupling constant	<b>7b</b>	<b>7c</b>	<b>7d</b>
$J_{2a,2b}$	13.8	15.0	12.5
$J_{2a,3}$	7.9	10.9	10.3
$J_{2b,3}$	4.9	4.0	4.0
$J_{3,4}$	9.2	10.9	10.1
$J_{4,5}$	7.9	7.6	8.7
$J_{5,6}$	6.0	—	5.8
$J_{6,7a}$	8.8	6.1	8.7
$J_{6,7b}$	3.8	10.0	6.2
$J_{7a,7b}$	13.1	13.5	13.2
$J_{7a,8}$	3.6	11.0	7.2
$J_{7b,8}$	8.5	9.5	11.2
$J_{3',4'}$	3.2	3.2	3.1
$J_{4',5'}$	1.9	2.0	1.9

Table 4 reveals that compounds **7b** and **7d** adopt similar structures. Naturally, though, the position of protons H-8 and H-3' in the furyl ring are reversed for isomer **7d** compared to isomer **7b** [**7b**: (8*S*), **7d**: (8*R*)]. This was confirmed by the coupling constants measured between protons H-6, H-7 and H-8 (Table 3). The only real difference between their structures is that proton H-7b is located closer to protons H-2a and H-4 in isomer **7d** (evaluated from the dihedral angles). Thus, for isomer **7d**, a cross-correlation peak was visible in the NOESY spectrum (H-7b/H-2a/H-4). In the case of isomer **7c**, protons H-3'/H-3/H-7a and H-5/H-3/H-7a on the top face of the oxazepane ring are found to be in close proximity to each other, according to the

Table 4. NOESY data of compounds **7b–7d**

Compd	Connected protons (upside positions) <sup>a</sup>	Connected protons (downside positions) <sup>a</sup>	Connected protons (peripheral positions) <sup>a</sup>
<b>7b</b>	H-3...H-2b; H-5...H-6	H-7b...H-8...H-4; H-8...H-2a...H-4	H-6...H-7a; H-7a...H-3'
<b>7c</b>	H-3'...H-3...H-7a H-3...H-5...H-7a H-3...H-2b	H-2a...H-4	H-7b...H-8; H-7b...H-6
<b>7d</b>	H-3...H-2b; H-5...H-6	H-7b...H-2a...H-4...H-3'	H-7a...H-6; H-7a...H-8

<sup>a</sup> Relative to the 9-oxa-1-azabicyclo[4.2.1]nonane skeleton as shown in Figure 6.

NOESY spectrum recorded. By taking into account the coupling constants for all the isoxazolidine and 1,2-oxazepane ring protons in all three isomers, we have been able to determine the configuration of each of the newly formed chiral centres [**7b**: (6*S*,8*S*); **7c**: (6*R*,8*S*); and **7d**: (6*S*,8*R*) (Fig. 4)]. The stereochemistry of the remaining chiral centres have been deduced from D-glucose and the conformation of the 1,2-oxazepane ring.

The effects of different Lewis acid catalysts ( $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{ZnCl}_2$ ,  $\text{MgCl}_2$ ), solvents, absence or presence of 4 Å molecular sieves and reflux time on yields and diastereomeric ratios for this intramolecular 1,3-dipolar cycloaddition with nitrone **6** (Fig. 3) have been examined in detail (Table 5). The diastereomeric ratios of **7b–7d** obtained from each reaction were initially determined by the combined use of TLC and RP-HPLC. However, as this method proved cumbersome and inaccurate, alternatives were sought. The fortunate finding that, in the  $^1\text{H}$  NMR spectra, the peaks assigned to protons H-3' and H-4' of the furyl ring were located in unique positions for each of the three isomers, that is, **7b–7d**, led us to investigate using  $^1\text{H}$  NMR spectroscopy instead for these measurements. This afforded ratios which were in good agreement with those obtained previously from RP-HPLC experiments and so, due to its convenience and accuracy, it became the method of choice.

From Table 5, it can be seen that when the intramolecular 1,3-dipolar cycloaddition was performed in toluene, the reflux time (24 or 48 h) had no effect on yield or diastereomeric ratio. However, since nitrone **6** decomposed quickly at temperatures above 100 °C, even under an argon atmosphere, it was not advantageous to heat the reaction in toluene at reflux for more than 24 h. 1,4-Dioxane was found to be an unsuitable solvent for this reaction; the mixture of isomers **7b–7d** was afforded in only 17% yield.

We have established that the main diastereoisomer obtained from these cycloaddition reactions (except when 1,4-dioxane and  $\text{ZnCl}_2$  was used) was **7b**, bearing the (6*S*,8*S*) configuration at the newly formed chiral centres (Table 5). The maximum yield for this intramolecular 1,3-dipolar cycloaddition was achieved when  $\text{MgCl}_2$  was added [90%, toluene, 120 °C (bath temperature), 12 h, Table 5]. Unexpectedly, in the presence of the harder Lewis acid catalyst,  $\text{BF}_3 \cdot \text{OEt}_2$ , most of the starting nitrone **6** decomposed after only a few hours to give an undesired product which contained one less benzoyl group (as determined from MS data). As a result of this finding, we propose that this also attributed to the reduced yield observed for the reaction performed in the presence of  $\text{ZnCl}_2$ , although here decomposition of the nitrone was slower.

In conclusion, we have ascertained that the optimum conditions for performing this 1,3-dipolar cycloaddition



**Table 5.** The effect of Lewis acids and solvents on yields and diastereomeric ratios

Solvent, mol sieves	Catalyst	Time (h)	Temperature (°C) <sup>a</sup>	Yield (%)	Diastereomeric ratios (HPLC) <sup>b</sup>	Diastereomeric ratios (NMR) <sup>b,c</sup>
Toluene, 4 Å	—	24	120	70	2.8:1:1	3:1:1
Toluene	—	48	120	75	2.8:1:1.2	3:1:1
Benzene, 4 Å	—	24	80	32	2.1:1:1	2:1:1
1,4-Dioxane, 4 Å	—	24	100	17	1:1.1:1.2	— <sup>d</sup>
Toluene, 4 Å	ZnCl <sub>2</sub>	24	120	50	4:1:1 <sup>e</sup>	0.5:1:1
Toluene, 4 Å	MgCl <sub>2</sub>	12	120	90	2:1:1	2:1:1
Toluene, 4 Å	BF <sub>3</sub> ·OEt <sub>2</sub>	24	120	— <sup>f</sup>	—	—

<sup>a</sup> Bath temperature.<sup>b</sup> Ratio of isomers **7b**:**7c**:**7d** isolated from the reaction mixture.<sup>c</sup> Determined from the integral of protons H-3' and H-4'.<sup>d</sup> Not determined due to the presence of impurities.<sup>e</sup> Diastereomer **7b** could not be separated from an impurity.<sup>f</sup> The starting material decomposed and a by-product was formed (see text).

reaction with nitron **6** (Fig. 3) involve using toluene as the solvent and MgCl<sub>2</sub> as the Lewis acid catalyst. It appears that if the Lewis acid catalyst added is hard, a side reaction involving elimination of a benzoyl protecting group from the starting nitron becomes significant and this may be accompanied by decomposition and conversion of the furyl group, too. The stereoselectivity of the cycloaddition was found not to alter much under the conditions investigated here.

### 3. Theoretical investigations

In order to analyse the geometry of all four diastereoisomers of the isoxazolidine derivative (i.e., **7a–7d** (Fig. 4)) produced from the intramolecular 1,3-dipolar cycloaddition with nitron **6** (Fig. 3), we have conducted a systematic computational investigation. This involved performing molecular dynamics simulations followed by high-level *ab initio* calculations. For the molecular dynamics studies, the 'simulated annealing' protocol described in the SYBYL program package<sup>19</sup> was employed to obtain the required starting geometries for isomers **7a–7d** for the subsequent higher level investigations. The Merck's force field parameter set (MMFF94) was applied with its own charge distribution. The molecules were equilibrated for 2000 fs at 1200 K and then cooled to 50 K exponentially over 10,000 fs. In this way, 1000 conformations were provided for each isomer. Next a semi-empirical optimization using the PM3 method was performed and the results afforded were grouped according to their energies. Finally, *ab initio*

calculations were conducted on a representative for each of the different energy clusters. These utilised the Hartree–Fock method with 3-21 Gaussian basis set and applied the Gaussian03 code.<sup>20</sup> Although this is one of the simplest methods, it was reasoned that this was sufficient for our purposes. The conformations of the oxazepane rings for isomers **7b–7d** derived from the computational studies were found to be in very good agreement with the structures obtained previously from NMR studies. In Figure 6, the optimized geometry of isomer **7b** is presented. The spatial proximity of protons H-7b, H-8, H-4 and H-2a on the bottom face can be clearly seen. In addition to the theoretical calculations providing information about the geometry of isomers **7a–7d**, we had hoped that they could also be used to predict the diastereomeric ratio afforded by the cycloaddition reaction (**7a**:**7b**:**7c**:**7d** ≈ 0:3:1:1) based on the total energy of each of the isomers.

However, it appeared that, at this level of theory, significant differences could not be observed with the total energies for diastereoisomers **7a–7d** being approximately the same. In Table 6, the HF/3-21G total energies of the minimized geometries for each of the different isoxazolidine isomers are presented.

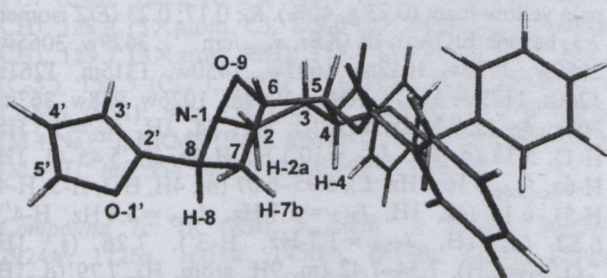
**Table 6.** Calculated total energies of compounds **7a–7d**<sup>a</sup>

Compound	Total energy (hartree)
<b>7a</b>	–1870.388634
<b>7b</b>	–1870.389014
<b>7c</b>	–1870.389014
<b>7d</b>	–1870.389272

<sup>a</sup> *Ab initio* (HF/3-21G method).

### 4. Conclusion

We have successfully synthesized a variety of isoxazolidine derivatives of chiral moieties employing a Lewis acid-catalyzed 1,3-dipolar cycloaddition. In our preliminary studies, the exclusive formation of 9-oxa-1-azabicyclo-[4.2.1]nonane diastereomers **7b–7d** (Fig. 4) from nitron **6** (Fig. 3) has been observed. The maximum yield for the 1,3-dipolar cycloaddition reaction was achieved with MgCl<sub>2</sub> as the Lewis acid catalyst [toluene, 120 °C (bath temperature), 12 h]. The ratio of the diastereoisomers of **7b–7d** was 3:1:1 and this did not alter significantly under the different



**Figure 6.** The lowest-energy conformation of compound **7b** calculated by HF/3-21 method. Proximal hydrogen atoms of 9-oxa-1-azabicyclo[4.2.1]nonane skeleton, supporting the configuration and conformation of the above compound (NMR evidence), are shown with the H prefix. Carbon atoms of the above skeleton and those of the furan skeleton (primed numbers) are labelled without the C prefix for clarity.



reaction conditions investigated here. The theoretical total energies of the minimized geometries for **7a–7d** obtained computationally failed to rationalise the experimentally determined diastereomeric ratios of these cycloadducts produced from the intramolecular 1,3-dipolar cycloaddition. Further studies are in progress to obtain chiral 1,2,4-substituted azetidines from the cycloadducts afforded and new cycloaddition reactions are envisaged.

## 5. Experimental

### 5.1. General procedures

The following abbreviations are employed: ACN (acetonitrile); ANA (azetidine nucleic acid(s)); anh. (anhydrous); Bn (benzyl); Bz (benzoyl);  $\text{CDCl}_3$  (deuteriochloroform);  $\text{CH}_2\text{Cl}_2$  (dichloromethane); ESI (electrospray ionization); EtOAc (ethyl acetate); FAB (fast atom bombardment); HRMS (high resolution mass spectrometry); LRMS (low resolution mass spectrometry); MeOD (deuteromethanol); MeOH (methanol); PNA [peptide nucleic acid(s)]; rt (room temperature); THF (tetrahydrofuran).

Chemicals were purchased from Aldrich, Fluka, Merck or Reanal (Budapest, Hungary). 2-Furaldehyde and  $\text{BF}_3 \cdot \text{OEt}_2$  were freshly distilled prior to use. Anhydrous solvents and anhydrous Lewis acid catalysts were prepared as described.<sup>21</sup> Organic solutions were dried using anhydrous  $\text{MgSO}_4$  and evaporated in Büchi rotary evaporators. TLC: Kieselgel 60 F<sub>254</sub> (Merck), solvent systems:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , hexane/EtOAc, visualization: UV light,  $\text{H}_2\text{SO}_4/\text{ethanol}$ . Mp: Electrothermal IA 8103 apparatus. IR spectra: Bio-Rad FTS-60A (KBr pellets unless otherwise stated,  $\nu_{\text{max}}/\text{cm}^{-1}$ , s, strong; m, medium; w, weak). NMR: Bruker Avance DRX 400 and 500 spectrometers ( $^1\text{H}$ : 400.13, 500.13 MHz;  $^{13}\text{C}$ : 125.76 MHz, respectively), MeOD,  $\text{CDCl}_3$  solutions,  $\delta$  (ppm),  $J$  (Hz). Spectral patterns: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; br, broad; deut, deuterable. The superscripts \*, # denote interchangeable assignments. For the 2D experiments (HSQC, HMBC, NOESY) the standard Bruker software packages (INV4GSSW, INV4GSLRNDWS) were applied. LRMS: Finnigan MAT TSQ 7000, ESI technique. HRMS: VG ZAB SEQ high resolution mass spectrometer using FAB ion source. Samples were dissolved in glycerol, the resolution of the instrument was 10,000. TLC/MS; TLC/HPLC: the analyte solution has been applied onto a 5 cm wide silica gel TLC plate as a band to obtain sufficient material. After developing in a solvent system the appropriate band was removed, the silica gel was suspended in MeOH (100  $\mu\text{L}$  for MS, 1000  $\mu\text{L}$  for HPLC), sonicated, centrifuged and the supernatant was used for MS analysis and HPLC (for HPLC 10  $\mu\text{L}$  was injected). HPLC: SHIMADZU UV/VIS detector: SPD-10A VP, pump: LC-10AC VP, column: LiChrospher 6.1, RP select B (5  $\mu\text{m}$ ). Eluent system: gradient: 70–90% ACN within 25 min, flow rate: 1 mL/min.

**5.1.1. (2S,3S,4R)-1-(Hydroxyimino)hex-5-ene-2,3,4-triyltribenzoate (4).** The unsaturated aldehyde **3**<sup>11</sup> (5.00 g, 10.92 mmol, 1 equiv) was dissolved in ethanol (100 mL) and distilled water (30 mL). The solution was treated with

hydroxylamine hydrochloride (3.41 g, 41.19 mmol, 4.5 equiv) and sodium hydrogen carbonate (3.41 g, 49.80 mmol, 4.6 equiv). After 2 h stirring at room temperature, the ethanol was removed under reduced pressure, and the residue was dissolved in dichloromethane (100 mL). The solution was washed with water (3  $\times$  50 mL), dried ( $\text{MgSO}_4$ ) and evaporated in vacuo. Further purification was accomplished by column chromatography [10%–50% (v/v) EtOAc in hexane] to give oxime **4** as a light yellow oil (5.16 g, 70%, 1:1 mixture of *E* and *Z* isomers).  $R_f$ : 0.60; 0.53 (*E/Z* isomer), (1:1, hexane/EtOAc); IR (film,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3426m, 3069w, 2984w, 1726s, 1601m, 1450m, 1315m, 1260s, 1246s, 1177m, 1105s, 1094s, 1069s, 1026m, 942w, 710s;  $\delta_{\text{H}}$  (500 MHz,  $\text{CH}_3\text{OD}$ ): 5.36 (m, 2H, H-6a, H-6b), 6.02 (m, 4H, H-2, H-3, H-4, H-5), 6.60 (m, 1H, H-1, *E*) 6.80 (d, 1H,  $J_{1,2}=5.4$  Hz, H-1, *Z*), 7.34–7.56 (m, 9H, arom. H), 7.96–8.04 (m, 6H, arom. H), 8.63 (s, 1H, OH).  $\delta_{\text{C}}$  (125 MHz,  $\text{CH}_3\text{OD}$ ): 68.1 (C-2, *Z*), 71.8 (C-2, *E*), 73.8 (C-3, *Z*), 74.5 (C-3, *E*), 74.6 (C-4, *E*), 74.8 (C-4, *Z*), 120.4 (C-6, *E*), 121.0 (C-6, *Z*), 129.6–129.7 (6  $\times$  arom. CH), 130.7 (3  $\times$  arom. C<sub>q</sub>), 130.8 (6  $\times$  arom. CH), 132.7 (C-5, *Z*), 134.6 (C-5, *E*), 134.7 (3  $\times$  arom. CH), 145.9 (C-1, *E*) 147.0 (C-1, *Z*), 166.6 (C=O), 166.7 (C=O), 167.1 (C=O); LRMS (ESI):  $m/z$  474 (57%,  $[\text{M}+\text{H}]^+$ ), 491 (100%,  $[\text{M}+\text{NH}_4]^+$ ), 496 (75%,  $[\text{M}+\text{Na}]^+$ ); HRMS (FAB, glycerol): Calcd for  $\text{C}_{27}\text{H}_{24}\text{NO}_7$   $[\text{M}+\text{H}]^+ m/z$  474.15473, found  $m/z$  474.15418.

**5.1.2. (2S,3S,4R)-2,3,4-Tris(benzoyloxy)-N-(furan-2-ylmethylene)hex-5-en-1-amine oxide (6).** To a stirred solution of oxime **4** (0.50 g, 1.06 mmol, 1 equiv) in dioxane (5 mL) was added sodium cyanoborohydride (0.22 g, 3.20 mmol, 3 equiv) in small portions, while the solution was carefully treated with HCl/dioxane (1.7 M,  $\sim$  1 mL), to maintain the pH between 3 and 5. After completion of reaction (TLC), the solution was evaporated in vacuo, the residue was dissolved in EtOAc (50 mL), the organic layer was washed with aqueous sodium carbonate (40 mL), water (40 mL) and brine (40 mL), dried ( $\text{MgSO}_4$ ) and evaporated in vacuo. The resulting hydroxylamine **5** was used without any further purification.

Compound **5** was dissolved in toluene (20 mL) and treated with freshly distilled 2-furaldehyde (176  $\mu\text{L}$ , 2.12 mmol) in the presence of 4 Å molecular sieves. After stirring at 50 °C for 18 h, the solution was filtered, evaporated under reduced pressure and co-evaporated with ACN (3  $\times$  50 mL). The crude residue was purified by column chromatography (10–30% (v/v) EtOAc in hexane) to give nitrone isomers **6** as a pale yellow foam (0.23 g, 40%).  $R_f$ : 0.17; 0.23 (*E/Z* isomer, 7:3, hexane/EtOAc); IR (KBr,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3429w, 3065w, 2980w, 1728s, 1612m, 1601w, 1450w, 1315m, 1261s, 1240s, 1179w, 1107s, 1096s, 1069m, 1026w, 948w, 863m, 708s;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ): 4.31 (d, 1H,  $J_{1,2}=5.5$  Hz, H-1), 5.35 (d, 1H,  $J_{5,6b}=10.1$  Hz H-6b, *Z*), 5.45 (d, 1H, H-6a,  $J_{5,6a}=16.6$  Hz, *E*), 5.95–6.07 (m, 4H, H-2, H-3, H-4, H-5), 6.16 (dd, 1H,  $J_{3',4'}=1.7$  Hz,  $J_{4',5'}=3.4$  Hz, H-4'), 6.52 (d, 1H,  $J_{3',4'}=1.7$  Hz, H-3'), 7.26 (s, 1H,  $^-\text{O}^+\text{N}=\text{CH}$ ), 7.34–7.42 (m, 9H, arom. H), 7.79 (d, 1H,  $J_{4',5'}=3.4$  Hz, H-5'), 7.97–8.04 (m, 6H, arom. H).  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ): 65.3 (C-1), 69.5 (C-2), 73.0 (C-4\*), 73.5 (C-3\*), 112.4 (C-3'), 116.3 (C-4'), 120.7 (C-6), 127.3 (CH=N), 128.4 (3  $\times$  arom. CH), 128.5 (3  $\times$  arom. CH), 128.6 (arom. C<sub>q</sub>), 129.7 (3  $\times$  arom. CH), 129.9 (3  $\times$  arom.



CH), 131.5 (C-5), 133.2 (arom. CH), 133.5 (2×arom. CH), 144.0 (C-5'), 146.3 (C-2'), 165.1 (C=O), 165.3 (C=O), 165.7 (C=O); LRMS (ESI):  $m/z$  554 (100%, [M+H]<sup>+</sup>), 576 (20%, [M+Na]<sup>+</sup>); HRMS (FAB, glycerol): Calcd for C<sub>32</sub>H<sub>28</sub>NO<sub>8</sub> [M+H]<sup>+</sup>  $m/z$  554.18094, found  $m/z$  554.18324.

**5.1.3. (3S,4R,5S,6S,8S)-8-(Furan-2-yl)-9-oxa-1-azabicyclo[4.2.1]nonane-3,4,5-triyl tribenzoate (7b); (3S,4R,5S,6R,8S)-8-(furan-2-yl)-9-oxa-1-azabicyclo[4.2.1]nonane-3,4,5-triyl tribenzoate (7c) and (3S,4R,5S,6S,8R)-8-(furan-2-yl)-9-oxa-1-azabicyclo[4.2.1]nonane-3,4,5-triyl tribenzoate (7d).** *General procedure.* The pure nitron 6 (0.40 g, 0.72 mmol) was dissolved in dry toluene (20 mL) in the presence of 4 Å molecular sieves and the solution was heated at 80–100–120 °C (bath temperature) for 12–48 h under an argon atmosphere. The reaction mixture was cooled, filtered, evaporated in vacuo and co-evaporated with ACN (3×50 mL). Chromatographic purification [0–10% (v/v) EtOAc in hexane], yielded three isomers (7b,7c,7d) as an oil or foam, in different isomer ratios depending on the reaction conditions, in 17–90% yield (Table 6). The ratios of the three diastereoisomers were determined by TLC, RP-HPLC and <sup>1</sup>H NMR (Table 6). The reactions were carried out under different conditions, for example, solvents, temperature, reflux time and with or without Lewis acid catalysts (see Table 5). The catalysts, anh. ZnCl<sub>2</sub>, anh. MgCl<sub>2</sub> and freshly distilled BF<sub>3</sub>·OEt<sub>2</sub>, were used in 0.1–0.2 mol equiv with respect to nitron. R<sub>f</sub>: 0.32 (7:3, hexane/EtOAc as a single spot; after 5× development in an 8:2, hexane/EtOAc eluent it could be separated into three isomers).

**Compound 7b:** IR (KBr,  $\nu_{\max}/\text{cm}^{-1}$ ): 3429w, 3065w, 2961w, 1726s, 1601w, 1450w, 1315m, 1281s, 1261s, 1179w, 1107s, 1096s, 1069m, 1026w, 708s;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>): 2.75 (ddd, 1H,  $J_{7a,7b}$  = 13.1 Hz,  $J_{6,7a}$  = 8.8<sup>#</sup> Hz,  $J_{7a,8}$  = 3.6<sup>#</sup> Hz, H-7a), 3.18 (ddd, 1H,  $J_{7a,7b}$  = 13.1 Hz,  $J_{7b,8}$  = 8.5<sup>#</sup> Hz,  $J_{6,7b}$  = 3.8<sup>#</sup> Hz, H-7b), 3.22 (dd, 1H,  $J_{2a,2b}$  = 13.8 Hz,  $J_{2a,3}$  = 7.9 Hz, H-2a), 4.22 (dd, 1H,  $J_{2a,2b}$  = 13.8 Hz,  $J_{2b,3}$  = 4.9 Hz, H-2b), 4.63 (dd, 1H,  $J_{7b,8}$  = 8.5<sup>#</sup> Hz,  $J_{7a,8}$  = 3.6<sup>#</sup> Hz, H-8), 5.02 (m, 1H, H-6), 5.68 (dd, 1H,  $J_{4,5}$  = 7.9 Hz,  $J_{5,6}$  = 6.0 Hz, H-5), 5.85 (m, 1H, H-3), 6.00 (dd, 1H,  $J_{3,4}$  = 9.2 Hz,  $J_{4,5}$  = 7.9 Hz, H-4), 6.28 (d, 1H,  $J_{3',4'}$  = 3.2 Hz, H-3'), 6.32 (dd, 1H,  $J_{3',4'}$  = 3.2 Hz,  $J_{4',5'}$  = 1.9 Hz, H-4'), 7.24–7.50 (m, 10H, arom. H, H-5'), 7.86–8.00 (m, 6H, arom. H);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>): 34.2 (C-7), 58.7 (C-2), 65.4 (C-8), 68.8 (C-3), 73.1 (C-4, C-5), 77.7 (C-6), 106.2 (C-3'), 110.3 (C-4'), 128.3 (3×arom. CH), 128.4 (3×arom. C), 129.6 (3×arom. C<sub>q</sub>), 3×arom. CH), 129.7 (3×arom. CH), 133.2 (3×arom. CH), 142.3 (C-5'), 154.3 (C-2'), 165.0 (C<sub>q</sub>), 165.1 (C<sub>q</sub>), 165.6 (C<sub>q</sub>); LRMS (ESI):  $m/z$  554 (100%, [M+H]<sup>+</sup>), 576 (50%, [M+Na]<sup>+</sup>); HRMS (FAB, glycerol): Calcd for C<sub>32</sub>H<sub>28</sub>NO<sub>8</sub> [M+H]<sup>+</sup>  $m/z$  554.18094, found  $m/z$  554.18213.

**Compound 7c:** IR (KBr,  $\nu_{\max}/\text{cm}^{-1}$ ): 3433w, 3063w, 2924w, 1726s, 1601w, 1450m, 1315m, 1281s, 1271s, 1179w, 1107s, 1069m, 1026m, 710s;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>): 2.83 (ddd, 1H,  $J_{7a,7b}$  = 13.5 Hz,  $J_{7a,8}$  = 11.0 Hz,  $J_{6,7a}$  = 6.1 Hz, H-7a), 2.89 (dd, 1H,  $J_{2a,2b}$  = 15.0 Hz,  $J_{2b,3}$  = 4.0 Hz, H-2b), 3.14 (ddd, 1H,  $J_{7a,7b}$  = 13.5 Hz,  $J_{6,7b}$  = 10.0 Hz,  $J_{7b,8}$  = 9.5 Hz, H-7b), 3.60 (dd, 1H,  $J_{2a,2b}$  = 15.0 Hz,  $J_{2a,3}$  = 10.9 Hz, H-2a), 4.74 (dd, 1H,

$J_{7a,8}$  = 11.0 Hz,  $J_{7b,8}$  = 9.5 Hz, H-8), 4.82 (dd, 1H,  $J_{6,7b}$  = 10.0 Hz,  $J_{6,7a}$  = 6.1 Hz, H-6), 5.51 (d, 1H,  $J_{4,5}$  = 7.6 Hz, H-5), 5.96 (ddd, 1H,  $J_{3,4}$  = 10.9 Hz,  $J_{2a,3}$  = 10.9 Hz,  $J_{2b,3}$  = 4.0 Hz, H-3), 6.21 (dd, 1H,  $J_{3,4}$  = 10.9 Hz,  $J_{4,5}$  = 7.6 Hz, H-4), 6.44 (dd, 1H,  $J_{3',4'}$  = 3.2 Hz,  $J_{4',5'}$  = 2 Hz, H-4'), 6.60 (d, 1H,  $J_{3',4'}$  = 3.2 Hz, H-3'), 7.19–7.54 (m, 9H, arom. H, 1H, H-5'), 7.75–8.00 (m, 6H, arom. H);  $\delta_{\text{C}}$  (125.76 MHz, CDCl<sub>3</sub>): 38.1 (C-7), 54.7 (C-2), 60.9 (C-8), 68.1 (C-3), 79.2 (C-5), 74.7 (C-4), 81.8 (C-6), 110.8 (C-4') 111.2 (C-3'), 127.6 (3×arom. CH), 127.9 (3×arom. CH), 129.0 (3×arom. CH, 3×arom. C<sub>q</sub>), 132.5 (3×arom. CH), 132.9 (3×arom. CH), 143.6 (C-5'), 147.1 (C-2'), 164.3 (C<sub>q</sub>), 165.1 (C<sub>q</sub>), 165.7 (C<sub>q</sub>); LRMS (ESI):  $m/z$  554 (100%, [M+H]<sup>+</sup>), 576 (43%, [M+Na]<sup>+</sup>); HRMS (FAB, glycerol): Calcd for C<sub>32</sub>H<sub>28</sub>NO<sub>8</sub> [M+H]<sup>+</sup>  $m/z$  554.18094, found  $m/z$  554.18268.

**Compound 7d:** IR (KBr,  $\nu_{\max}/\text{cm}^{-1}$ ): 3067w, 2928w, 1730s, 1601w, 1450w, 1315w, 1281s, 1260s, 1179w, 1109m, 1096m, 1070m, 1026w, 710m;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>): 2.67 (ddd, 1H,  $J_{7a,7b}$  = 13.2 Hz,  $J_{6,7a}$  = 8.7 Hz,  $J_{7a,8}$  = 7.2 Hz, H-7a), 2.86 (ddd, 1H,  $J_{7a,7b}$  = 13.2 Hz,  $J_{7b,8}$  = 11.2 Hz,  $J_{6,7b}$  = 6.2 Hz, H-7b), 3.02 (dd, 1H,  $J_{2a,2b}$  = 12.5 Hz,  $J_{2a,3}$  = 10.3 Hz, H-2a), 3.53 (dd, 1H,  $J_{2a,2b}$  = 12.5 Hz,  $J_{2b,3}$  = 4.0 Hz, H-2b), 4.71 (dd, 1H,  $J_{7a,8}$  = 7.2 Hz,  $J_{7b,8}$  = 11.2 Hz, H-8), 4.96 (ddd, 1H,  $J_{6,7a}$  = 8.7 Hz,  $J_{6,7b}$  = 6.2 Hz,  $J_{5,6}$  = 5.8 Hz, H-6), 5.89 (ddd, 1H,  $J_{2a,3}$  = 10.3 Hz,  $J_{3,4}$  = 10.1 Hz,  $J_{2b,3}$  = 4.0 Hz, H-3), 5.69 (dd, 1H,  $J_{4,5}$  = 8.7 Hz,  $J_{5,6}$  = 5.8 Hz, H-5), 5.98 (dd, 1H,  $J_{3,4}$  = 10.1 Hz,  $J_{4,5}$  = 8.7 Hz, H-4), 6.42 (dd, 1H,  $J_{3',4'}$  = 3.1 Hz,  $J_{4',5'}$  = 1.9 Hz, H-4'), 6.51 (d, 1H,  $J_{3',4'}$  = 3.1 Hz, H-3'), 7.20–7.25 (m, 3H, arom. H), 7.39–7.41 (m, 3H, arom. H), 7.49–7.52 (m, 4H, arom. H, H-5'), 7.78–7.82 (m, 3H, arom. H), 7.97–7.99 (m, 3H, arom. H);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>): 31.2 (C-7), 52.2 (C-2), 64.1 (C-8), 66.8 (C-3), 73.2 (C-5), 74.6 (C-4), 77.6 (C-6), 111.1 (C-3'), 110.7 (C-4'), 128.1, 128.2 (3×arom. CH), 128.5 (3×arom. C<sub>q</sub>), 129.6 (3×arom. CH) 129.8 (3×arom. CH), 133.0 (3×arom. CH), 133.4 (3×arom. CH), 143.4 (C-5'), 148.1 (C-2'), 165.0 (C<sub>q</sub>), 165.4 (C<sub>q</sub>), 165.9 (C<sub>q</sub>); LRMS (ESI):  $m/z$  554 (100%, [M+H]<sup>+</sup>), 576 (56%, [M+Na]<sup>+</sup>); HRMS (FAB, glycerol): Calcd for C<sub>32</sub>H<sub>28</sub>NO<sub>8</sub> [M+H]<sup>+</sup>  $m/z$  554.18094, found  $m/z$  554.18379.

NOESY data: Table 4.

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## II.







# Stereoselective synthesis of pyrrolidinyl glycines from nitrones: complementarity of nucleophilic addition and 1,3-dipolar cycloaddition

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**Abstract**—Epimeric pyrrolidinyl glycines, a sort of conformationally constrained  $\alpha,\beta$ -diaminoacids, were stereoselectively prepared using complementary approaches based on nitrone chemistry. Nucleophilic additions to pyrrolidinyl nitrones and 1,3-dipolar cycloadditions of L-serine derived nitrones to form the corresponding hydroxylamines and isoxazolidines, respectively, provided key intermediates for the synthesis of the target compounds. Whereas the nucleophilic addition route afforded the *syn* adduct, the 1,3-dipolar cycloaddition approach furnished the precursor for the preparation of the corresponding *anti* compound.

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$\alpha,\beta$ -Diaminoacids **1** are interesting targets because of their utility as synthetic intermediates as well as their presence in several biologically active compounds.<sup>1</sup> In addition, much attention was focused during the last years on the preparation of conformationally constrained amino acids.<sup>2</sup> A recent surge of activity into the synthetic chemistry of hetaryl glycines, in particular, tetrahydrofuran derivatives is also indicative of the importance of this area.<sup>3</sup>

Pyrrolidinyl glycines **2** can be considered as conformationally restricted  $\alpha,\beta$ -diamino acids whose preparation is still scarcely considered. To the best of our knowledge, such compounds have only been synthesized in particular cases. Compounds **3** have been used as synthetic intermediates for the preparation of bicyclic piperazine 2-carboxylic acids<sup>4</sup> that have been further utilized in asymmetric synthesis as either catalysts or building blocks.<sup>5</sup> Bicyclic pyrrolidinyl glycines **4** have also been employed as intermediates in the synthesis of models for the azinomycin<sup>6</sup> and ficellomycin<sup>7</sup> antibiotics (Fig. 1).

As a part of our continuing research program on the synthetic potential of nitrones, and in the preparation of non-proteinogenic aminoacids,<sup>8</sup> including  $\alpha,\beta$ -diamino acids,<sup>9</sup> we now report on two new complementary routes leading to epimers at the  $\beta$ -stereogenic center of pyrrolidinyl glycines.

The synthetic approaches are based on nitrone chemistry and they make use of the two different and well-known reactivities of the nitrone functionality in 1,3-dipolar cycloadditions and nucleophilic additions.<sup>10</sup>

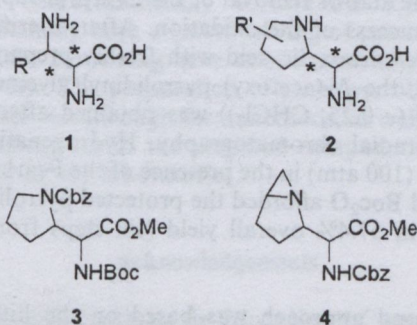
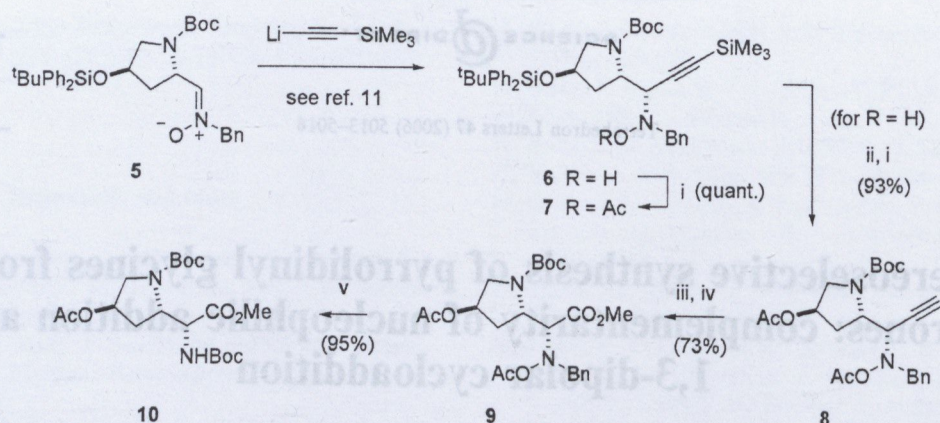


Figure 1.

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**Scheme 1.** Reagents and conditions: (i)  $\text{Ac}_2\text{O}$ , Py, rt; (ii)  $\text{Bu}_4\text{NF}$ , THF, rt; (iii)  $\text{RuCl}_3$ ,  $\text{NaIO}_4$ ,  $\text{CH}_3\text{CN}-\text{CCl}_4-\text{H}_2\text{O}$  (3:2:2), rt; (iv)  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ , rt; (v)  $\text{H}_2$ , 100 atm,  $\text{Pd}(\text{OH})_2-\text{C}$ ,  $\text{Boc}_2\text{O}$ , rt.

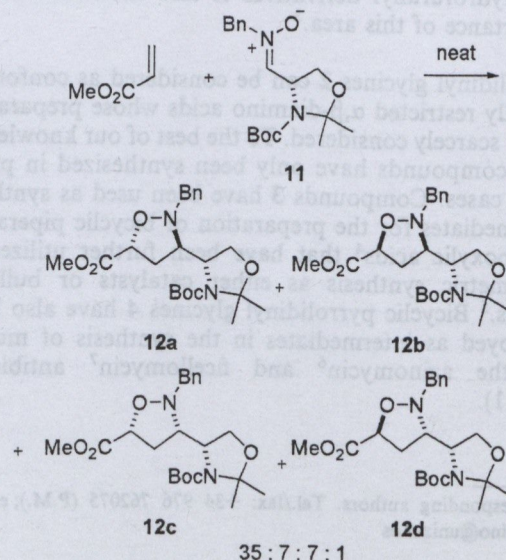
Our first approach started from the completely stereoselective addition of lithium trimethylsilyl acetylide to the pyrrolidinylnitrone **5** (Scheme 1). Only one isomer could be detected in the reaction mixture and compound **6** ( $[\alpha]_D^{+5}$  ( $c$  0.21,  $\text{CHCl}_3$ )) was obtained in 93% chemical yield.<sup>11</sup> The stereochemical course of the reaction can be explained on the basis of our previously reported model for nucleophilic additions of Grignard reagents to pyrrolidinylnitrones.<sup>12</sup> The absolute configuration of **6** was unambiguously assigned following our previously reported empirical rule based on NMR measurements.<sup>13</sup> After protection of the *N*-hydroxyamino group as an acetyl derivative, compound **7** (100%;  $[\alpha]_D^{-27}$  ( $c$  0.41,  $\text{CHCl}_3$ )) was obtained. Unfortunately, all attempts of oxidizing the ethynyl group to a carboxylic acid either with  $\text{RuO}_2$  or  $\text{RuCl}_3$  in the presence of an excess of sodium periodate as a reoxidant, failed; only decomposition products were recovered from the reaction mixtures. A similar behavior had already been observed in our laboratory.<sup>14</sup> Thus the silyl groups in **6** were cleaved with TBAF in THF and after acetylation of the resulting crude product, compound **8** (89%;  $[\alpha]_D^{-37}$  ( $c$  0.38,  $\text{CHCl}_3$ )) was obtained.

In this case, unmasking of the carboxyl moiety was carried out by oxidation of the triple bond with the system  $\text{RuCl}_3-\text{NaIO}_4$  in good yield, thus demonstrating that the replacement of the *O*-silyl protecting group by the acetyl one and/or removal of the *C*-silyl group is crucial for the success of the oxidation. After esterification of the crude carboxylic acid with freshly prepared diazomethane, the *N*-(acetoxy) pyrrolidinylnitrone **9** (73%;  $[\alpha]_D^{-39}$  ( $c$  0.25,  $\text{CHCl}_3$ )) was obtained after purification by radial chromatography. Hydrogenation under pressure (100 atm) in the presence of the Pearlman's catalyst and  $\text{Boc}_2\text{O}$  afforded the protected pyrrolidinylnitrone **10** in 57.4% overall yield (six steps from nitrone **5**).<sup>15</sup>

Our second approach was based on the hitherto unknown 1,3-dipolar cycloaddition between the L-serine derived nitron **11** and methyl acrylate (Scheme 2). The reaction was conducted without solvent at 90 °C in a sealed tube for 5 h. The NMR analysis of the crude

mixture revealed the presence of four isomers in 35:7:7:1 ratio, which was further confirmed by HPLC (XTerra C18, 5  $\mu\text{m}$ ,  $\text{MeOH}-\text{H}_2\text{O}$ , 3:2). After separation of the adducts by OPLC (OPLC-50, 0.2 mm HTSorb™ 5  $\mu\text{m}$  silica gel layer, hexane/ $\text{EtOAc}$  8:2, 50 bar, 500  $\mu\text{L}/\text{min}$ ) the major adduct **12a** was obtained in 56% isolated yield.<sup>16</sup> The stereochemical assignment of **12a-d** was determined by careful NMR analysis utilizing homonuclear decoupling, multiple-difference NOE and 2D experiments including COSY, ROESY, and HMQC.

Moreover, the observed stereochemical induction is in agreement with previous observations for  $\alpha$ -alkoxy and  $\alpha$ -amino nitrones for which, in all cases, the diastereofacial induction showed to be *anti* with respect to the heteroatom in  $\alpha$  position to the nitron moiety.<sup>17</sup> Tentatively, we suggest that this stereochemical outcome is in agreement with the transition state model A illustrated in Figure 2 corresponding to an *endo* approach of the dipolarophile to the *Re* face of the nitron.



**Scheme 2.** Cycloaddition between **11** and methyl acrylate.



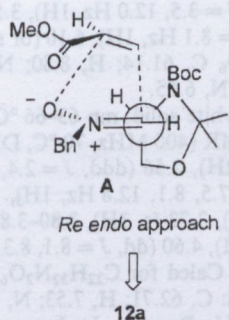
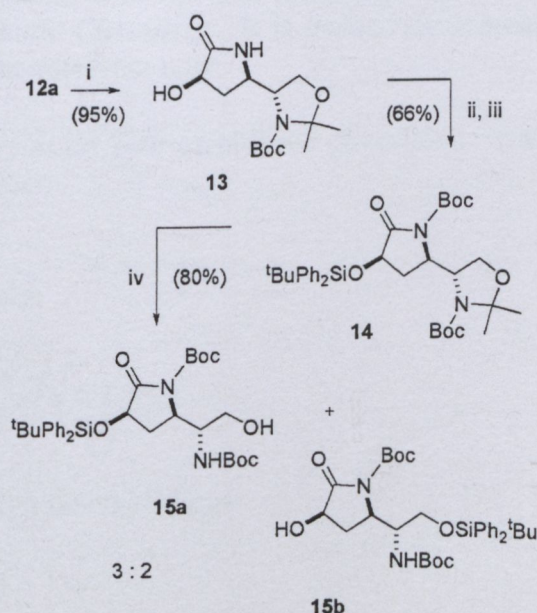


Figure 2. Proposed model for the 1,3-dipolar cycloaddition between **11** and methyl acrylate.

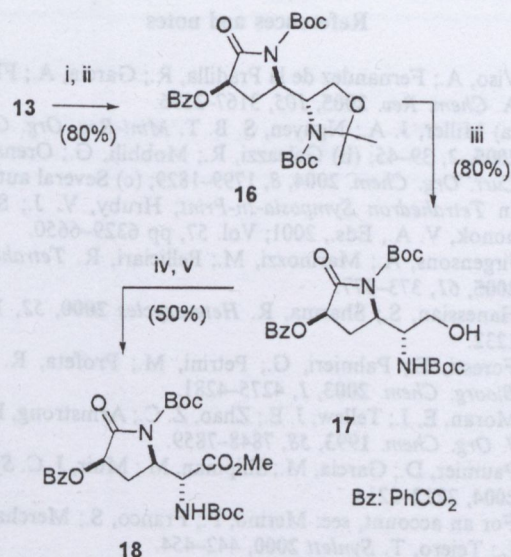
Catalytic hydrogenation of **12a** using Pearlman's catalyst provided pyrrolidinone **13** ( $[\alpha]_D -33$  ( $c$  0.21,  $\text{CHCl}_3$ ); mp 164–166 °C) in 95% yield (Scheme 3).

Compound **13** was treated with *tert*-butyldiphenyl silyl chloride and  $\text{Boc}_2\text{O}$  to afford the protected pyrrolidin-2-one **14** ( $[\alpha]_D +34$  ( $c$  0.22,  $\text{CHCl}_3$ )). However, acidic hydrolysis of the oxazolidine moiety to liberate the primary hydroxyl group as a previous step for the oxidation reaction afforded a 3:2 mixture of the expected compound **15a** ( $[\alpha]_D +25$  ( $c$  0.17,  $\text{CHCl}_3$ )) and **15b** ( $[\alpha]_D -6$  ( $c$  0.30,  $\text{CHCl}_3$ )), the latter coming from an unexpected silyl migration.

In order to avoid the silyl migration, we then decided to change the protecting group of the hydroxyl group. After benzylation and N-protection of **13**, compound **16** (80%,  $[\alpha]_D +45$  ( $c$  0.25,  $\text{CHCl}_3$ )) was obtained as the immediate precursor of the target compound (Scheme 4). Treatment of **16** with catalytic *p*-TsOH in methanol gave rise to the free primary alcohol **17** (80%,  $[\alpha]_D +20$  ( $c$  0.27,  $\text{CHCl}_3$ )) which was subsequently



Scheme 3. Reagents and conditions: (i)  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2\text{-C}$ , 100 atm, rt; (ii)  $^t\text{BuPh}_2\text{SiCl}$ , imidazole, DMF, 70 °C; (iii)  $\text{Boc}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ; (iv) *p*-TsOH, MeOH, 45 °C, 6 h.



Scheme 4. Reagents and conditions: (i)  $\text{PhCOCl}$ , Py,  $\text{CH}_2\text{Cl}_2$ , 0 °C; (ii)  $\text{Boc}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ; (iii) *p*-TsOH, MeOH, 45 °C, 6 h; (iv) TEMPO, [bis(acetoxy)iodo]benzene, MeCN– $\text{H}_2\text{O}$ ; (v)  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ , rt.

oxidized with the system TEMPO-BAIB<sup>18</sup> to afford the crude carboxylic acid. This compound was isolated and fully characterized<sup>19</sup> as the corresponding methyl ester **18** which was obtained by treatment of the acid with an ethereal solution of freshly prepared diazomethane. Compound **18** was obtained in 17% overall yield (seven steps from nitrene **11**).

We also attempted the reduction of the lactam moiety in compound **18** to obtain the corresponding saturated pyrrolidine, following the Garcia-Ruano's procedure.<sup>20</sup> Unfortunately, the reduction failed and only the starting compound was obtained.<sup>21</sup>

In conclusion, two complementary routes leading to *syn*- and *anti*-pyrrolidinyl glycines via a nucleophilic addition to nitrene **5** and a cycloaddition reaction of **11** with methyl acrylate, respectively, have been achieved. In the first approach, an ethynyl group has been used as a synthetic equivalent of the carboxyl unit. For the second approach, the synthetic equivalence between the oxazolidine ring and the glycine unit has been utilized. Unusual conformationally constrained  $\alpha,\beta$ -diaminoacids containing both a saturated ring of pyrrolidine and a pyrrolidin-2-one ring have been successfully prepared in this work. The preparation of other pyrrolidinyl glycines of interest through these methods, as well as chemical modifications of the prepared compounds are now underway in our laboratories.

#### Acknowledgements

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15. Data for **10**: oil,  $[\alpha]_D -54$  (c 0.11, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, 100 °C, DMSO-*d*<sub>6</sub>): δ 1.42 (s, 9H), 1.44 (s, 9H), 1.96 (s, 3H), 2.10–2.30 (m, 2H), 3.06 (dd, *J* = 3.8, 12.0 Hz, 1H), 3.15 (dd, *J* = 3.5, 12.0 Hz, 1H), 3.59 (s, 3H), 4.10 (m, 1H), 4.70 (d, *J* = 8.1 Hz, 1H), 6.10 (br s, 1H). Anal. Calcd for C<sub>21</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub>: C, 61.14; H, 8.80; N, 6.79. Found: C, 61.37; H, 8.61; N, 6.55.
16. Data for **12a**: white solid; mp 63–66 °C.  $[\alpha]_D -54$  (c 0.11, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, 70 °C, DMSO-*d*<sub>6</sub>): δ 1.44 (s, 3H), 1.45 (s, 12H), 2.56 (ddd, *J* = 2.4, 8.3, 12.8 Hz, 1H), 2.63 (ddd, *J* = 7.5, 8.1, 12.8 Hz, 1H), 3.45 (ddd, *J* = 2.4, 7.4, 7.5 Hz, 1H), 3.72 (s, 3H), 3.80–3.83 (m, 4H), 4.07 (d, *J* = 13.6 Hz, 1H), 4.60 (dd, *J* = 8.1, 8.3 Hz, 1H), 7.26–7.30 (m, 5H). Anal. Calcd for C<sub>22</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>: C, 62.84; H, 7.67; N, 6.66. Found: C, 62.71; H, 7.53; N, 6.70.
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18. Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293–295.
19. Data for **18**: oil,  $[\alpha]_D -2$  (c 0.13, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, 70 °C, DMSO-*d*<sub>6</sub>): δ 1.39 (s, 9H), 1.50 (s, 9H), 2.04 (ddd, *J* = 6.3, 6.7, 13.7 Hz, 1H), 2.52–2.54 (m, 1H), 3.70 (s, 3H), 4.54–4.56 (m, 1H), 5.03 (dd, *J* = 3.5, 9.1 Hz, 1H), 5.56 (dd, *J* = 6.7, 9.8 Hz, 1H), 7.01 (d, *J* = 9.1 Hz, 1H), 7.50–7.54 (m, 2H), 7.67–7.70 (m, 1H), 8.02–8.05 (m, 2H). Anal. Calcd for C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>9</sub>: C, 58.53; H, 6.55; N, 5.69. Found: C, 58.49; H, 6.60; N, 5.76.
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21. Quite probably the reaction conditions are too mild for performing the reaction, and other conditions could lack of chemoselectivity with the different ester functionalities present in the molecule. This reduction step should be attempted at an earlier stage (i.e., with compound **13**) in order to have some guarantee of success. We are currently studying this possibility and it will be reported in due course.



### III.

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Dear Dr. Kovács:

RE: Manuscript Number JO061503B - note

AUTHORS: Petra Pádár, Attila Bokros, Gábor Paragi, Péter Forgó, Zoltán Kele, Nicola M. Howarth, Lajos Kovács

TITLE: Single diastereomers of polyhydroxylated 9-oxa-1-azabicyclo[4.2.1]nonanes from intramolecular 1,3-dipolar cycloaddition of  $\omega$ -unsaturated nitrones

I am pleased to advise you that your revised manuscript has been accepted for publication in the *Journal of Organic Chemistry*. It is tentatively scheduled to appear in an issue to be published approximately three months from now.

Thank you for your careful job of revision. We look forward to receiving future contributions from your laboratory.

Sincerely,

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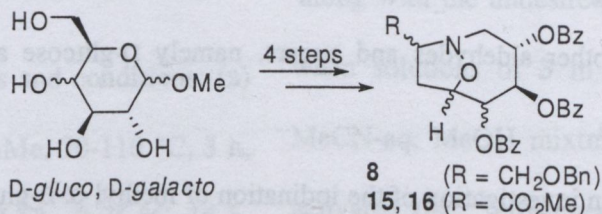


# Single diastereomers of polyhydroxylated 9-oxa-1-azabicyclo[4.2.1]nonanes from intramolecular 1,3-dipolar cycloaddition of $\omega$ -unsaturated nitrones

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**Abstract.** 8-Benzyloxymethyl-3,4,5-tribenzoyloxy-9-oxa-1-azabicyclo[4.2.1]nonane has been prepared as a single diastereoisomer **8** from an intramolecular 1,3-dipolar cycloaddition involving 2-(benzyloxy)acetaldehyde and  $\omega$ -unsaturated hydroxylamine **7** derived from methyl  $\alpha$ -D-glucopyranoside. The analogous 8-methoxycarbonyl 9-oxa-1-azabicyclo[4.2.1]nonane was afforded in a similar manner, from methyl D-galactopyranoside and methyl glyoxylate, as a 3:1 mixture of diastereoisomers **15** and **16**. When conducted in achiral ionic liquid **17** this ratio increased to 8:1 and, in chiral ionic liquid **18**, compound **15** was formed exclusively.



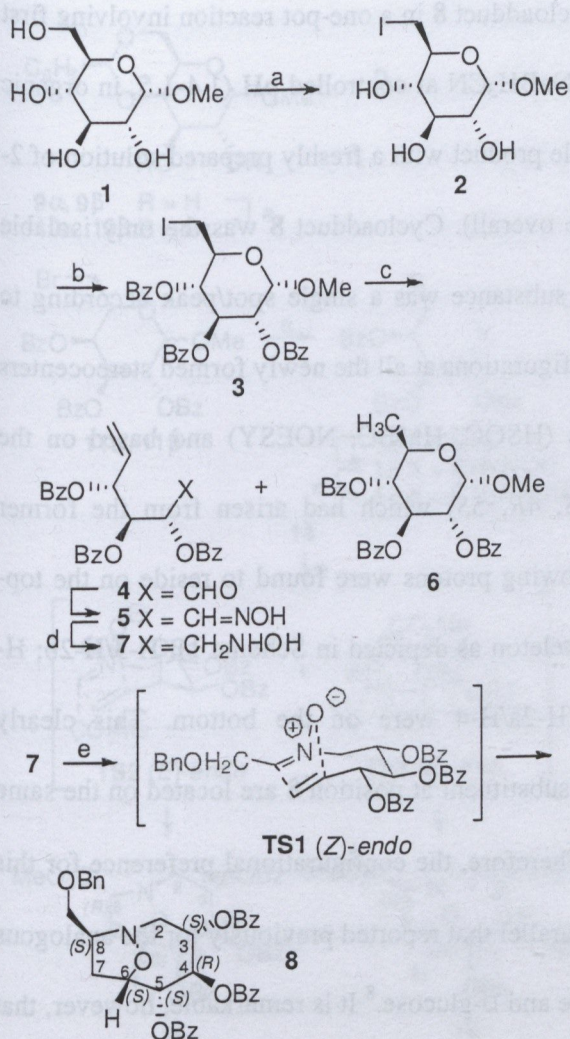
Glycosidases are intimately involved in a plethora of metabolic pathways and the development of glycosidase inhibitors presents an enormous challenge for the treatment of associated disorders, *e.g.* diabetes, Gaucher's disease, cancer and viral infections including AIDS.<sup>1-5</sup> Recently, highly oxygenated chiral heterocycles containing nitrogen (also referred to as azasugars, iminosugars or iminocyclitols) have emerged as potential glycosidase inhibitors worthy of further investigation.<sup>6,7</sup>

Our interest in this field stems from our previous synthetic efforts to prepare chiral azetidines. *En route* to these compounds, diastereomeric mixtures of hydroxylated chiral 9-oxa-1-azabicyclo[4.2.1]nonanes were produced through an intramolecular 1,3-dipolar cycloaddition involving  $\omega$ -unsaturated nitrones derived from D-glucose and 2-furaldehyde.<sup>8</sup> This nitrone-alkene cycloaddition is a well-known powerful tool which has successfully been employed in the literature to construct a variety of isoxazolidines, 1,3-aminoalcohols and derivatives<sup>9,10</sup> usually starting from carbohydrate precursors.<sup>11,12</sup> Recently, a ring-contracted dihydroxylated 8-oxa-1-azabicyclo[3.2.1]octane and its ring-opened azepane derivative have been found to be effective glycosidase inhibitors.<sup>13</sup>

As highlighted above, due to the increasing biological interest in this class of compounds, we have decided to explore the scope of this intramolecular 1,3-dipolar cycloaddition. Therefore, we have investigated the utility of other aldehydes and sugars, namely D-glucose and D-galactose, and our findings are presented herein.

Thus, we first embarked on investigation of the iodination of methyl  $\alpha$ -D-glucopyranoside **1** using the conditions described by Vasella<sup>14-16</sup> and Garegg<sup>17</sup> (Scheme 1). After extensive experimentation, we have found that iodo compound **2** can only be obtained reproducibly in good yields (60%) on a large scale when using a modified procedure which requires careful consideration of reaction conditions (*e.g.* reagent addition times, temperature, stirring) and combination of different purification procedures. Subsequent benzylation of compound **2**<sup>18-20</sup> successfully afforded benzoate **3**.<sup>21-23</sup> The latter halo derivative **3** was then subjected to the Boord-Vasella reaction<sup>14-16,24-28</sup> (which involved treatment with activated zinc in various solvents, under sonication).





**SCHEME 1.** Reagents and conditions: (a)  $\text{Ph}_3\text{P}$ ,  $\text{I}_2$ , imidazole,  $\text{PhMe}$ , 70-110 °C, 3 h, 60%; (b)  $\text{BzCl}$ ,  $\text{py}$ ,  $\text{CH}_2\text{Cl}_2$ , 0-25 °C, 16 h, 85%; (c) 1.  $\text{Zn}$ , various solvents, sonication, 40-60 °C, 4-5 h, 2.  $\text{NH}_2\text{OH}\cdot\text{HCl}$ , aq.  $\text{Na}_2\text{CO}_3$ ,  $\text{CH}_2\text{Cl}_2$ , **5**: 0-65%, **6**: 27-85%; (d)  $\text{NaBH}_3\text{CN}$ , dioxane,  $\text{MeOH}$ ,  $\text{pH}=1.4-1.5$ , rt, 45 min; (e)  $\text{BnOCH}_2\text{CHO}$ ,  $\text{PhMe}$ , 4 Å mol. sieves, 110 °C, 20 h, 28% overall

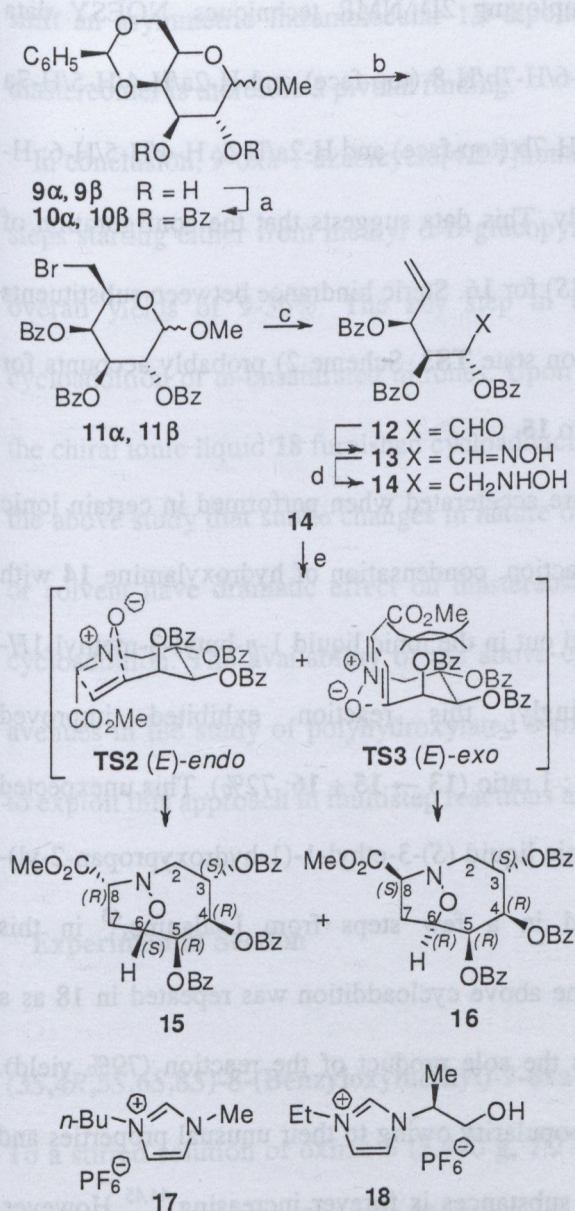
Surprisingly, despite the fact that there are numerous publications in the literature dealing with this reaction,<sup>14-16,22,23,29,30</sup> an experimentally simple and reliable method suitable for the production of  $\omega$ -unsaturated aldehyde **4** could not easily be established. We reported previously that, although many different reaction conditions worked well on small scale, increasing the scale of transformation was typically accompanied with a considerable decrease in product yield.<sup>8</sup> We also noted, in the present case, that the nature of solvent had a dramatic effect both on yield and chemoselectivity of the reaction. That is to say, aldehyde **4** (isolated as a stable oxime **5**,<sup>8</sup> 1:1 *E/Z* mixture) was consistently afforded in 55-65% yield along with the undesired side product **6**<sup>31,32</sup> (27-32%) when solutions of **3** in THF-aq. MeOH or THF or MeCN-aq. MeOH mixtures were treated with  $\text{CeCl}_3$ -activated zinc.<sup>23</sup> However, in neat dioxane, the yield of compound **5** was drastically reduced (12%) while the yield of the concurrent 6-deoxy derivative **6** substantially increased (75%) and in other neat solvents (DMF, MeCN, acetone, di-*i*-propyl ether) compound **6** was produced exclusively (85%). Fürstner *et al.*<sup>22</sup> have likewise noted that less reactive halo derivatives (*e.g.* 6-bromo-6-deoxysugars) are prone to reduction.



Finally, oxime **5** was successfully transformed into cycloadduct **8** in a one-pot reaction involving first reduction to the corresponding hydroxylamine **7** using NaBH<sub>3</sub>CN at controlled pH (1.4-1.5, in organic phase) followed by condensation of the resulting unstable product with a freshly prepared solution of 2-(benzyloxy)acetaldehyde<sup>33</sup> in dry toluene (**5** → **8**; 28% overall). Cycloadduct **8** was the only isolable compound from the reaction mixture and the purified substance was a single spot/peak according to TLC, OPLC and HPLC. The gross structure and the configurations at all the newly formed stereocenters were assigned using 1D and 2D NMR measurements (HSQC, HMBC, NOESY) and based on the known configuration of pre-existing stereocenters (3*S*, 4*R*, 5*S*) which had arisen from the former carbohydrate moiety. In the NOESY spectrum the following protons were found to reside on the top-face (relative to the 9-oxa-1-azabicyclo[4.2.1]nonane skeleton as depicted in Scheme 1): H-3/H-2b; H-5/H-6; H-6/H-7b while protons H-7a/H-8/H-4; H-8/H-2a/H-4 were on the bottom. This clearly demonstrates that proton H-6 and the benzyloxymethyl substituent at position 8 are located on the same side (β<sup>−</sup>) and their absolute configuration is (6*S*, 8*S*). Therefore, the configurational preference for this intramolecular 1,3-dipolar cycloaddition was found to parallel that reported previously for the analogous reaction employing a nitron derived from 2-furaldehyde and D-glucose.<sup>8</sup> It is remarkable, however, that changing a substituent from 2-furyl to benzyloxymethyl at position 8 affects drastically the diastereoselectivity of this 1,3-dipolar cycloaddition: with 2-furyl substituent three difficult-to-separate diastereomers were obtained<sup>8</sup> whereas the benzyloxymethyl substituent directed the reaction to the exclusive formation of single diastereomer **8**. The formation of the alternative regioisomer (an 8-oxa-1-azabicyclo[4.2.1]nonane with a bridgehead methyne group) was not observed. It is generally assumed that in such cycloadditions the new C-C bond is more developed in the transition state than the C-O bond (*cf.* Scheme 1, **TS1**) and hence both for steric and electronic reasons, the C-C bond is preferably formed at the less substituted alkene position,<sup>8,13,34,35</sup> although the effects of substituents and ring-sizes on the regioselectivity show significant variation.<sup>34,36,37</sup>

In order to expand the repertoire for this reaction we have investigated the corresponding intramolecular 1,3-dipolar cycloaddition for a nitron prepared from methyl D-galactopyranoside. In this





**SCHEME 2.** Reagents and conditions: (a) BzCl, py, CH<sub>2</sub>Cl<sub>2</sub>, 0–25 °C, 4 h, 90%; (b) NBS, BaCO<sub>3</sub>, CHCl<sub>3</sub>, ClCH<sub>2</sub>CH<sub>2</sub>Cl, 65 °C, 3 h, 70%; (c) 1. Zn, cat. CeCl<sub>3</sub>, NH<sub>4</sub>Cl, MeOH, THF, sonication, 40 °C, 3 h, 2. NH<sub>2</sub>OH·HCl, aq. K<sub>2</sub>CO<sub>3</sub>, Et<sub>2</sub>O, rt, 16 h, 72% overall; (d) NaBH<sub>3</sub>CN, MeOH, pH=1.4–1.5, rt, 1 h; (e) MeO<sub>2</sub>CCHO, 4Å mol. sieves, 110 °C, 20 h, PhMe or **17** or **18**, 64–79%

case, functionalization required a slightly different approach as direct halogenation of methyl D-galactopyranoside at position 6 proved to be problematic due to steric hindrance exerted by the axial hydroxyl group at position 4. Thus, compound **9**<sup>38</sup> (Scheme 2), which was readily available from methyl D-galactopyranoside, was utilized instead. Following benzylation, **10**<sup>39</sup> was subjected to Hanessian-type oxidative ring opening<sup>40</sup> using NBS to afford the 6-bromo-6-deoxy derivative **11**, characterized as two separate epimers. The Boord-Vasella ring-opening of **11** gave aldehyde **12** (isolated as the stable oxime **13**, 2:1 *E/Z* mixture) in 72% yield. Occasionally, by-products from this reaction (*e.g.* the corresponding 6-deoxy pyranose) were also observed but, in most cases, this proved to be negligible. Oxime **13** was successfully reduced under identical conditions to those used above for the *D-gluco* derivative (NaBH<sub>3</sub>CN, MeOH, pH = 1.4–1.5) and the resulting hydroxylamine **14** was condensed without any further purification with a freshly prepared solution of methyl glyoxylate<sup>41</sup> in dry toluene. For this cycloaddition the intermediate nitrone yielded two cycloadducts, **15** and **16**, in a 3 : 1 ratio (**13** → **15** + **16**: 64%). Configurational assignment for all the



newly formed stereocenters was again performed employing 2D NMR techniques. NOESY data revealed the spatial proximity of protons H-2b/H-3; H-6/H-7b/H-8 (top-face) and H-2a/H-4/H-5/H-7a (bottom-face) for **15** and that of protons H-2b/H-3; H-3/H-7b (top-face) and H-2a/H-4; H-4/H-5/H-6; H-5/H-6/H-7a; H-7a/H-8 (bottom-face) for **16**, respectively. This data suggests that the configuration of newly formed stereocenters is (6*S*, 8*R*) for **15** and (6*R*, 8*S*) for **16**. Steric hindrance between substituents at C-5 and C-8 in **16** (and in the corresponding transition state **TS3**, Scheme 2) probably accounts for the sub-ordinate formation of this compound compared to **15**.

It has been reported that 1,3-dipolar cycloadditions are accelerated when performed in certain ionic liquids.<sup>42</sup> Thus, in an attempt to optimize the above reaction, condensation of hydroxylamine **14** with freshly prepared methyl glyoxylate has also been carried out in the ionic liquid 1-*n*-butyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate **17**. Surprisingly, this reaction exhibited improved diastereoselectivity with **15** and **16** being isolated in a 8 : 1 ratio (**13** → **15** + **16**: 72%). This unexpected finding prompted us to examine the use of the chiral ionic liquid (*S*)-3-ethyl-1-(1-hydroxypropan-2-yl)-1*H*-imidazol-3-ium hexafluorophosphate **18**, prepared in a few steps from L-alanine,<sup>43</sup> in this intramolecular 1,3-dipolar cycloaddition. Thus, when the above cycloaddition was repeated in **18** as a solvent, cycloadduct **15** was unexpectedly obtained as the sole product of the reaction (79% yield). Since their discovery, ionic liquids have gained much popularity owing to their unusual properties and interest to replace traditional solvents with these new substances is forever increasing.<sup>44,45</sup> However, although the application of ionic liquids in organic chemistry is rapidly expanding, there are currently only a few examples in the literature reporting the use of chiral ionic liquids in asymmetric reactions and the best asymmetric induction obtained so far was 44% ee.<sup>46,47</sup> One can expect a significant transfer of chirality in these solvents due to their high degree of organization. It has been reported that most of ionic liquids possess a polymeric structure and are highly ordered H-bonded liquids (three-dimensional networks of anions and cations linked together by hydrogen bonds).<sup>46</sup> In addition, it was recently shown that hydrogen bonding is involved in controlling the *endo*-selectivity of Diels–Alder reactions performed in achiral ionic liquids.<sup>48</sup> Thus, our unprecedented observation that a chiral ionic liquid can



shift an asymmetric intramolecular 1,3-dipolar cycloaddition to the exclusive formation of a single diastereomer is therefore a pivotal finding.

In conclusion, 9-oxa-1-azabicyclo[4.2.1]nonanes **8**, **15** and **16** have been successfully prepared in four steps starting either from methyl  $\alpha$ -D-glucopyranoside or methyl D-galactopyranoside, respectively, in overall yields of 9-36%. The key step in their synthesis involved an intramolecular 1,3-dipolar cycloaddition of  $\omega$ -unsaturated nitrones. Upon optimizing this reaction we have discovered that use of the chiral ionic liquid **18** furnished cycloadduct **15** as a single diastereomer in high yield. It is clear from the above study that subtle changes in nature of substituent and/or configuration of the starting nitrones or solvent have dramatic effect on diastereoselectivity of this asymmetric intramolecular 1,3-dipolar cycloaddition. The availability of the above cycloadducts in pure diastereomeric form opens up new avenues in the study of polyhydroxylated 9-oxa-1-azabicyclo[4.2.1]nonanes and further investigations to exploit this approach in multistep reactions are in progress and will be reported in due course.

## Experimental Section

**(3S,4R,5S,6S,8S)-8-(Benzyloxymethyl)-9-oxa-1-azabicyclo[4.2.1]nonane-3,4,5-triyl tribenzoate (8).**

To a stirred solution of oxime **5** (3.440 g, 7.27 mmol) in dioxane (300 mL) and MeOH (300 mL) was added  $\text{NaBH}_3\text{CN}$  (2.740 g, 43.60 mmol, 6 equiv.) while the solution was carefully treated with  $\text{HCl}$ /dioxane (1.7 M, ~30 mL) to maintain the pH between 1.4-1.5 using a combined pH glass electrode for organic solutions. After approximately 45 min, when the reduction stopped (the pH of the reaction mixture did not alter further), the solution was evaporated *in vacuo*, co-evaporated with MeCN (100 mL), the residue was dissolved in a mixture of EtOAc (400 mL) and satd. aq.  $\text{Na}_2\text{CO}_3$  solution (300 mL), the organic phase was washed with additional  $\text{Na}_2\text{CO}_3$  solution (300 mL), water (300 mL) and brine (300 mL), dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo*. If the reaction solution still contains some starting material **5** (TLC), subsequent  $\text{NaBH}_3\text{CN}$  (2.740 g, 43.60 mmol, 6 equiv.) has to be added and the pH must be maintained for a repeated 30 min period. The unstable hydroxylamine **7** was used



immediately without any further purification to avoid its decomposition.  $R_f$ : 0.60, hexanes : EtOAc 1 : 1; TLC-MS ( $m/z$ ): 476 (100%,  $[M+H]^+$ ), 498 (12,  $[M+Na]^+$ ). The above hydroxylamine **7** was dissolved in dry toluene (250 mL) and treated with freshly prepared 2-(benzyloxy)acetaldehyde (2 equiv.) in the presence of 4 Å molecular sieves and a Dean-Stark water trap. After stirring at 110 °C for 20 h, the solution was filtered, evaporated *in vacuo* and co-evaporated with MeCN (3 × 50 mL). The residue was purified by silica gel column chromatography [eluent: 0-5% (v/v) Et<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub>] to give the title cycloaddition product **8** as a pale yellow oil (1.22 g, 28% overall yield).  $R_f$ : 0.33, CH<sub>2</sub>Cl<sub>2</sub> : Et<sub>2</sub>O 95 : 5.  $[\alpha]_D$ : -26 (c=0.5, MeOH). IR (CaF<sub>2</sub>, thin film): 990 (w), 1026 (m), 1069 (m), 1096 (s), 1177 (w), 1261 (s), 1278 (s), 1315 (m), 1451 (m), 1493 (w), 1584 (w), 1601 (w), 1724 (s), 2859 (w), 2942 (w), 3030 (w), 3057 (w) cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>,  $\delta$ , ppm, superscripts \* and # denote interchangeable assignments) 2.25 (1H, ddd,  $J_{6,7b\#} = 8.7$  Hz,  $J_{7a,7b} = 13.5$  Hz,  $J_{7b,8\#} = 4.6$  Hz, H-7b); 2.96 (1H, ddd,  $J_{6,7a*} = 2.8$  Hz,  $J_{7a,7b} = 13.5$  Hz,  $J_{7a,8*} = 8.6$  Hz, H-7a); 3.14 (1H, dd,  $J_{2a,2b} = 14.1$  Hz,  $J_{2a,3} = 7.7$  Hz, H-2a); 3.41 (1H, dd,  $J_{8,1'a} = 6.4$  Hz,  $J_{1'a,1'b} = 9.4$  Hz, H-1'a); 3.60 (1H, dd,  $J_{8,1'b} = 7.3$  Hz,  $J_{1'a,1'b} = 9.4$  Hz, H-1'b); 3.75 (1H, m, H-8); 4.24 (1H, dd,  $J_{2a,2b} = 14.1$  Hz,  $J_{2b,3} = 5.5$  Hz, H-2b); 4.57 (1H, d,  $J_{2'a,2'b} = 11.9$  Hz, H-2'a); 4.66 (1H, d,  $J_{2'a,2'b} = 11.9$  Hz, H-2'b); 4.86 (1H, ddd,  $J_{5,6} = 5.8$  Hz,  $J_{6,7b\#} = 8.7$  Hz,  $J_{6,7a*} = 2.8$  Hz, H-6); 5.66 (1H, dd,  $J_{4,5} = 8.1$  Hz,  $J_{5,6} = 5.8$  Hz, H-5); 5.84 (1H, ddd,  $J_{2a,3} = 7.7$  Hz,  $J_{2b,3} = 5.5$  Hz,  $J_{3,4} = 9.4$  Hz, H-3); 5.99 (1H, dd,  $J_{3,4} = 9.4$  Hz,  $J_{4,5} = 8.1$  Hz, H-4); 7.37 (14H, m, arom.); 7.90 (6H, m, arom.). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>,  $\delta$ , ppm) 32.8 (C-7); 59.1 (C-2); 67.6 (C-8); 69.1 (C-3); 72.6 (C-4); 73.1 (C-1'); 73.2 (C-5); 73.4 (C-2'); 77.1 (C-6); 127.7-128.3 (arom.); 129.0 (arom. C<sub>q</sub>); 129.1 (arom. C<sub>q</sub>); 133.0 (arom.); 133.1 (arom.); 133.2 (arom.); 138.0 (arom. C<sub>q</sub>); 165.1 (CO); 165.1 (CO); 165.5 (CO). NOESY (connected protons, relative to the 9-oxa-1-azabicyclo[4.2.1]nonane skeleton), top-face: H-3/H-2b; H-5/H-6; H-6/H-7b; bottom-face: H-7a/H-8/H-4; H-8/H-2a/H-4. LRMS ( $m/z$ ): 608 (100%,  $[M+H]^+$ ), 630 (25,  $[M+Na]^+$ ). HRMS (FAB, glycerol): calcd. for C<sub>36</sub>H<sub>34</sub>NO<sub>8</sub><sup>+</sup>  $[M+H]^+$   $m/z$  608.22789, found  $m/z$  608.2310. Anal. calcd. for C<sub>36</sub>H<sub>33</sub>NO<sub>8</sub> (607.649) C, 71.16; H, 5.47; N, 2.31; found C, 71.03; H, 5.59; N, 2.48%.



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**Supporting Information Available:** Experimental procedures and characterization data for all compounds and copy of 1D  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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**Single diastereomers of polyhydroxylated 9-oxa-1-azabicyclo[4.2.1]nonanes from intramolecular 1,3-dipolar cycloaddition of  $\omega$ -unsaturated nitrones**

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**Supporting Information. Part 1 - Experimental procedures and spectral data**

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## General procedures

**Abbreviations:** equiv. (equivalent), LRMS (low resolution mass spectrometry); OPLC (overpressurised layer chromatography).

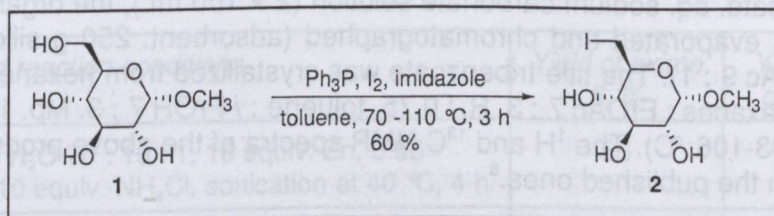
(*S*)-3-Ethyl-1-(1-hydroxypropan-2-yl)-1*H*-imidazol-3-ium hexafluorophosphate **18** was prepared as described.<sup>1</sup> Hexanes refer to a mixture of hexanes containing min. 55 % *n*-hexane. Anhydrous solvents were prepared as described.<sup>2</sup> Organic solutions were dried using anhydrous MgSO<sub>4</sub> and evaporated in rotary evaporators. TLC: Kieselgel 60 F<sub>254</sub>, visualization: UV light, iodine and/or charring with H<sub>2</sub>SO<sub>4</sub>/ethanol. Optical rotation: 589 nm, quartz cell (100 mm), 25 °C. pH-measurement: microprocessor pH meter combined with pH glass electrode for organic solutions. IR spectra: CaF<sub>2</sub>,  $\nu_{\max}/\text{cm}^{-1}$ , s, strong; m, medium; w, weak; br, broad. NMR: 400.13 MHz and 500.13 MHz (<sup>1</sup>H); 125.76 MHz (<sup>13</sup>C), respectively, CDCl<sub>3</sub> and C<sub>6</sub>D<sub>6</sub> solutions,  $\delta$  (ppm), *J* (Hz). The superscripts \*, # denote interchangeable assignments. For the 2D experiments (HSQC, HMBC, NOESY) the standard software packages (INV4GSSW, INV4GSLRND SW) were applied. LRMS: ESI technique. HRMS: high resolution sector instrument using FAB ion source. Samples were dissolved in glycerol, the resolution of the instrument was 10,000. TLC-MS: the analyte solution has been applied onto a 5 cm wide silica gel TLC plate as a band to obtain sufficient material. After developing in a solvent system the appropriate band was removed, the silica gel was suspended in MeOH (100  $\mu$ L), sonicated, centrifuged and the supernatant was used for MS analysis. OPLC: OPLC-50 (Bionisis, France), 0.2 mm thick HTSorb<sup>TM</sup> 5  $\mu$ m silica gel layers (OPLC-Nit Ltd., Hungary), hexane/EtOAc solvent mixtures, 50 bar, eluent flow: 500  $\mu$ L/min. HPLC: UV/VIS detector, column: LiChrospher 6.1, RP select B (5  $\mu$ m). Eluent system: gradient: 70-90% MeCN within 25 min, flow rate: 1 mL/min.

**Activation of zinc:** zinc powder (2.65 g, 40.60 mmol) was subsequently washed with 1 M HCl (3  $\times$  50 mL), water (50 mL), ethanol (50 mL) and Et<sub>2</sub>O (2  $\times$  50 mL). Sonication: in an ultrasonic bath (37 kHz, 275 W).

**2-(Benzyloxy)acetaldehyde** was freshly prepared using the procedure developed by Shiao *et al.*<sup>3</sup> and modified as follows. ( $\pm$ )-3-Benzyloxy-1,2-propanediol (3.32 g, 18.20 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (120 mL) and treated with sodium metaperiodate (9.73 g, 45.5 mmol, 5 equiv.) in water (240 mL). This solution was stirred for overnight at rt, the phases were then separated, the organic layer was dried (MgSO<sub>4</sub>), evaporated and the resulting oily 2-(benzyloxy)acetaldehyde was used without any further purification for the cycloaddition reactions.

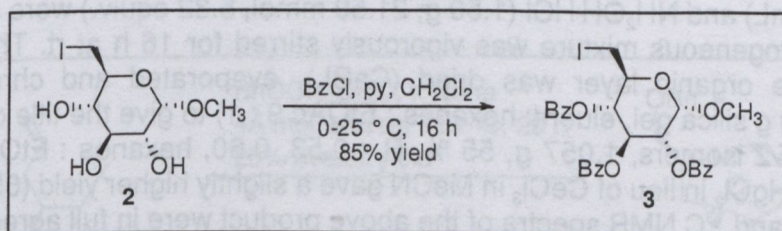


### Methyl 6-deoxy-6-iodo- $\alpha$ -D-glucopyranoside (**2**)<sup>4,5</sup>



A three-necked, 1 L flask was equipped with a condenser, a mechanical shaker and a stopper. The solution of methyl  $\alpha$ -D-glucopyranoside (10.00 g, 51.50 mmol) in toluene (300 mL) was agitated mechanically at room temperature while triphenylphosphine (20.24 g, 77.20 mmol, 1.50 equiv.) and imidazole (10.51 g, 154.92 mmol, 3.00 equiv.) were added portionwise. The mixture was heated to reflux then, after 1 h, cooled to 70 °C. Iodine (18.30 g, 72.10 mmol, 1.40 equiv.) was added portionwise under vigorous shaking and the initially brown mixture was vigorously agitated at 70 °C until the brown colour of iodine disappeared and then the mixture was heated at reflux for 3 h. The mixture was cooled in an ice-bath and extracted with water (5  $\times$  200 mL), the aq. phase was backwashed with toluene (100 mL). The combined organic phases were dried ( $\text{MgSO}_4$ ), evaporated and coevaporated with acetonitrile. The crude product (containing four spots according to TLC in toluene : *i*-PrOH 7 : 3, detection: UV, iodine vapor, and charring) was dissolved in hot ethanol (100 mL) and hot EtOAc (500 mL) was added. The resulting precipitate (imidazolium iodide) was removed by filtration and the filtrate was concentrated and subjected to column chromatography (adsorbent: 250 g silica gel, eluent: toluene : *i*-PrOH 9 : 1). The product was obtained as a semisolid which was then crystallized from a toluene-*i*-PrOH mixture. 9.396 g (60 %), mp. 145.8–146.2 °C (lit.<sup>6</sup> value: 146–147 °C),  $R_f$ : 0.30, toluene : *i*-PrOH 7 : 3. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the above product were in full agreement with the published ones.<sup>5</sup>

### Methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-benzoyl- $\alpha$ -D-glucopyranoside (**3**).<sup>7,8</sup>

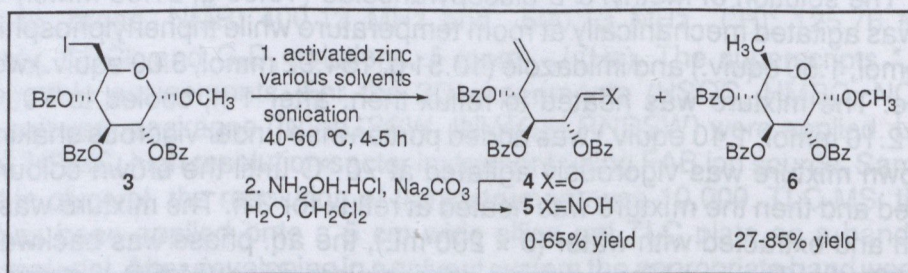


Methyl 6-deoxy-6-iodo- $\alpha$ -D-glucopyranoside (**2**, 10.00 g, 32.89 mmol) dissolved in anhydr. pyridine (65 mL) and anhydr.  $\text{CH}_2\text{Cl}_2$  (65 mL) was treated with benzoyl chloride (17.0 mL, 146.58 mmol, 4.46 equiv.) at 0 °C with stirring. After adding benzoyl chloride the mixture was allowed to warm to ambient temperature and stirring was continued at this



temperature for 16 h. The reaction mixture was evaporated and the residue was dissolved in EtOAc (500 mL), subsequently extracted with water (2 × 100 mL), aq. citric acid solution (2 × 100 mL), satd. aq. sodium carbonate solution (2 × 100 mL), the organic phase was dried (MgSO<sub>4</sub>), evaporated and chromatographed (adsorbent: 250 g silica gel, eluent: hexanes : EtOAc 9 : 1). The title tribenzoate was crystallized from hexanes, 17.22 g (85 %). *R<sub>f</sub>*: 0.30, hexanes : EtOAc 7 : 3, *R<sub>f</sub>*: 0.75, toluene : *i*-PrOH 7 : 3. Mp. 104.6-106.1 °C (lit.<sup>7,8</sup> value: 103-106 °C). The <sup>1</sup>H and <sup>13</sup>C NMR spectra of the above product were in full agreement with the published ones.<sup>8</sup>

**(*E/Z*)-5,6-Dideoxy-2,3,4-tri-*O*-benzoyl-*D*-xylo-hex-5-eno-5-oxime (5)<sup>9</sup> and methyl 6-deoxy-2,3,4-tri-*O*-benzoyl- $\alpha$ -*D*-glucopyranoside (6)<sup>10</sup>**



NH<sub>4</sub>Cl (2.17 g, 40.60 mmol, 10 equiv.) CeCl<sub>3</sub><sup>11</sup> (0.050 g, 0.20 mmol, 0.05 equiv.) and activated zinc (2.65 g, 40.60 mmol, 10 equiv.) in THF (10 mL) was allowed to react in an ultrasonic bath at 40 °C for 15 min. Methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-benzoyl- $\alpha$ -*D*-glucopyranoside **3** (2.50 g, 4.06 mmol) was dissolved in THF (60 mL) and poured into the zinc slurry and sonication was continued. This solution was often mixed with a spatula at the beginning of the reaction to prevent the coagulation of zinc dust. After 2 h MeOH (10 mL) and after an additional 1 h water (1 mL) were added to the reaction mixture to dissolve the zinc salts from the zinc surface. After 4 h sonication the mixture was chilled in an ice-bath, filtered, washed with EtOAc (150 mL), dried (CaCl<sub>2</sub>), evaporated *in vacuo* and the resulting aldehyde **4** (*R<sub>f</sub>*: 0.30, hexanes : EtOAc 7 : 3) was used without purification directly for the next step. The crude aldehyde **4** was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (200 mL), satd. aq. Na<sub>2</sub>CO<sub>3</sub> (100 mL) and NH<sub>2</sub>OH·HCl (1.50 g, 21.59 mmol, 5.32 equiv.) were added and the resulting heterogeneous mixture was vigorously stirred for 16 h at rt. The layers were separated, the organic layer was dried (CaCl<sub>2</sub>), evaporated and chromatographed (adsorbent: 30 g silica gel, eluent: hexanes : EtOAc 9 : 1) to give the title oily oximes (1 : 1 mixture of *E/Z* isomers, 1.057 g, 55 %, *R<sub>f</sub>*: 0.53, 0.60, hexanes : EtOAc 1 : 1). The application of HgCl<sub>2</sub> in lieu of CeCl<sub>3</sub> in MeCN gave a slightly higher yield (65 %, see Table 1). The IR, <sup>1</sup>H and <sup>13</sup>C NMR spectra of the above product were in full agreement with the published ones.<sup>9</sup>

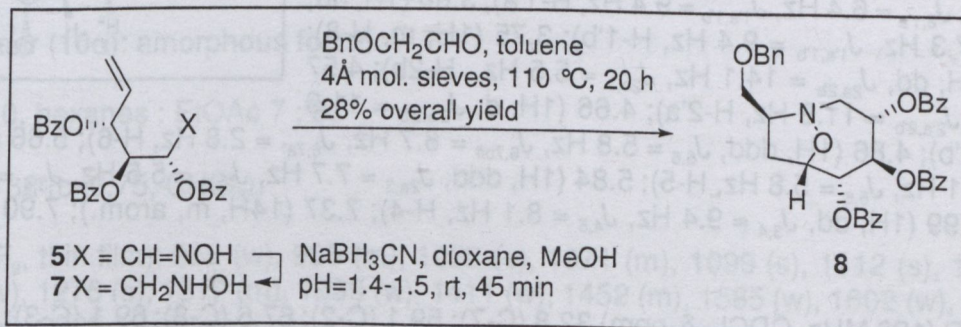
Along with the oxime the 6-deoxy derivative (**6**)<sup>10</sup> could also be isolated (*R<sub>f</sub>*: 0.30, hexanes : EtOAc 7 : 3, *R<sub>f</sub>*: 0.65, toluene : *i*-PrOH 7 : 3, mp 145.5-146.5 °C, lit.<sup>10</sup> value 139-140 °C) in variable amounts in different solvents (see Table 1).



Table 1. Yields of compounds **5** and **6** in the zinc-mediated reaction of 6-deoxy-6-iodo derivative **3**

Solvent(s) and reaction conditions	Yield of oxime <b>5</b> , %	Yield of 6-deoxy derivative <b>6</b> , %
THF : MeOH : H <sub>2</sub> O 70 : 10 : 1, 10 equiv. Zn, 0.05 equiv. CeCl <sub>3</sub> , 10 equiv. NH <sub>4</sub> Cl, sonication at 40 °C, 4 h	55	32
neat THF, 10 equiv. Zn, 0.05 equiv. CeCl <sub>3</sub> , 10 equiv. NH <sub>4</sub> Cl, sonication at 40 °C, 4 h	60	30
MeCN : MeOH : H <sub>2</sub> O 50 : 2.5 : 2.5, 10 equiv. Zn, 0.05 equiv. HgCl <sub>2</sub> , 10 equiv. NH <sub>4</sub> Cl, sonication at 40 °C for 30 min then reflux for 30 min and this cycle was repeated for 5 h	65	27
neat dioxane, 10 equiv. Zn, 0.05 equiv. CeCl <sub>3</sub> , 10 equiv. NH <sub>4</sub> Cl, sonication at 40 °C, 4 h	12	75
neat DMF, 10 equiv. Zn, 0.05 equiv. CeCl <sub>3</sub> , 10 equiv. NH <sub>4</sub> Cl, sonication at 40 °C, 4 h	0	85
neat MeCN, 10 equiv. Zn, 0.05 equiv. CeCl <sub>3</sub> , 10 equiv. NH <sub>4</sub> Cl, sonication at 40 °C, 4 h	0	85
neat acetone, 10 equiv. Zn, 0.05 equiv. CeCl <sub>3</sub> , 10 equiv. NH <sub>4</sub> Cl, sonication at 40 °C, 4 h	0	85
neat di- <i>i</i> -propyl ether, 10 equiv. Zn, 0.05 equiv. CeCl <sub>3</sub> , 10 equiv. NH <sub>4</sub> Cl, sonication at 40 °C, 4 h	0	85

**(3*S*,4*R*,5*S*,6*S*,8*S*)-8-(Benzyloxymethyl)-9-oxa-1-azabicyclo[4.2.1]nonane-3,4,5-triyl tribenzoate (**8**)**





To a stirred solution of oxime **5** (3.44 g, 7.27 mmol) in dioxane (300 mL) and MeOH (300 mL) was added  $\text{NaBH}_3\text{CN}$  (2.74 g, 43.60 mmol, 6 equiv.) while the solution was carefully treated with  $\text{HCl}$ /dioxane (1.7 M, ~30 mL) to maintain the pH between 1.4-1.5 using a combined pH glass electrode for organic solutions. After approximately 45 min, when the reduction stopped (the pH of the reaction solution did not alter further), the solution was evaporated *in vacuo*, co-evaporated with MeCN (100 mL), the residue was dissolved in a mixture of EtOAc (400 mL) and satd. aq.  $\text{Na}_2\text{CO}_3$  solution (300 mL), the organic phase was washed with additional  $\text{Na}_2\text{CO}_3$  solution (300 mL), water (300 mL) and brine (300 mL), dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo*. If the reaction solution still contains some starting material **5** (TLC), subsequent  $\text{NaBH}_3\text{CN}$  (2.74 g, 43.60 mmol, 6 equiv.) has to be added and the pH must be maintained for a repeated 30 min period. The unstable hydroxylamine **7** was used immediately without any further purification to avoid its decomposition.  $R_f$ : 0.60, hexanes : EtOAc 1 : 1; TLC-MS ( $m/z$ ): 476 (100%,  $[\text{M}+\text{H}]^+$ ), 498 (12,  $[\text{M}+\text{Na}]^+$ ).

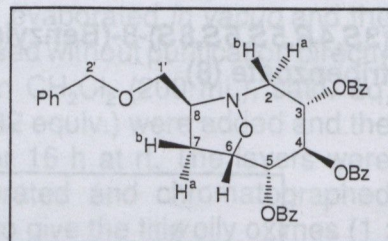
The above hydroxylamine **7** was dissolved in dry toluene (250 mL) and treated with freshly prepared 2-(benzyloxy)acetaldehyde (2 equiv.) in the presence of 4 Å molecular sieves and a Dean-Stark water trap. After stirring at 110 °C for 20 h, the solution was filtered, evaporated *in vacuo* and co-evaporated with MeCN (3 × 50 mL). The residue was purified by silica gel column chromatography [eluent: 0-5% (v/v)  $\text{Et}_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$ ] to give the title cycloaddition product **8** as a pale yellow oil (1.22 g, 28% overall yield).

$R_f$ : 0.33,  $\text{CH}_2\text{Cl}_2$  :  $\text{Et}_2\text{O}$  95 : 5.

$[\alpha]_D^{25}$ : -26 ( $c=0.5$ , MeOH).

IR ( $\text{CaF}_2$ , thin film): 990 (w), 1026 (m), 1069 (m), 1096 (s), 1177 (w), 1261 (s), 1278 (s), 1315 (m), 1451 (m), 1493 (w), 1584 (w), 1601 (w), 1724 (s), 2859 (w), 2942 (w), 3030 (w), 3057 (w)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ , ppm) 2.25 (1H, ddd,  $J_{6,7b\#} = 8.7$  Hz,  $J_{7a,7b} = 13.5$  Hz,  $J_{7b,8\#} = 4.6$  Hz, H-7b); 2.96 (1H, ddd,  $J_{6,7a\#} = 2.8$  Hz,  $J_{7a,7b} = 13.5$  Hz,  $J_{7a,8\#} = 8.6$  Hz, H-7a); 3.14 (1H, dd,  $J_{2a,2b} = 14.1$  Hz,  $J_{2a,3} = 7.7$  Hz, H-2a); 3.41 (1H, dd,  $J_{8,1'a} = 6.4$  Hz,  $J_{1'a,1'b} = 9.4$  Hz, H-1'a); 3.60 (1H, dd,  $J_{8,1'b} = 7.3$  Hz,  $J_{1'a,1'b} = 9.4$  Hz, H-1'b); 3.75 (1H, m, H-8); 4.24 (1H, dd,  $J_{2a,2b} = 14.1$  Hz,  $J_{2b,3} = 5.5$  Hz, H-2b); 4.57 (1H, d,  $J_{2'a,2'b} = 11.9$  Hz, H-2'a); 4.66 (1H, d,  $J_{2'a,2'b} = 11.9$  Hz, H-2'b); 4.86 (1H, ddd,  $J_{5,6} = 5.8$  Hz,  $J_{6,7b\#} = 8.7$  Hz,  $J_{6,7a\#} = 2.8$  Hz, H-6); 5.66 (1H, dd,  $J_{4,5} = 8.1$  Hz,  $J_{5,6} = 5.8$  Hz, H-5); 5.84 (1H, ddd,  $J_{2a,3} = 7.7$  Hz,  $J_{2b,3} = 5.5$  Hz,  $J_{3,4} = 9.4$  Hz, H-3); 5.99 (1H, dd,  $J_{3,4} = 9.4$  Hz,  $J_{4,5} = 8.1$  Hz, H-4); 7.37 (14H, m, arom.); 7.90 (6H, m, arom.).



$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ,  $\delta$ , ppm) 32.8 (C-7); 59.1 (C-2); 67.6 (C-8); 69.1 (C-3); 72.6 (C-4); 73.1 (C-1'); 73.2 (C-5); 73.4 (C-2'); 77.1 (C-6); 127.7-128.3 (arom.); 129.0 (arom.  $\text{C}_q$ );



129.1 (arom. C<sub>q</sub>); 133.0 (arom.); 133.1 (arom.); 133.2 (arom.); 138.0 (arom. C<sub>q</sub>); 165.1 (CO); 165.1 (CO); 165.5 (CO).

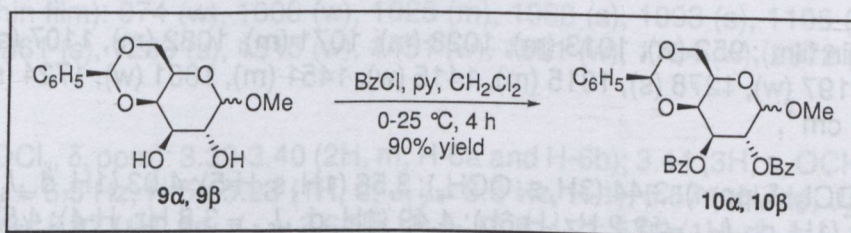
NOESY (connected protons, relative to the 9-oxa-1-azabicyclo[4.2.1]nonane skeleton)  
top-face: H-3/H-2b; H-5/H-6; H-6/H-7b;  
bottom-face: H-7a/H-8/H-4; H-8/H-2a/H-4.

LRMS (*m/z*): 608 (100%, [M+H]<sup>+</sup>), 630 (25, [M+Na]<sup>+</sup>).

HRMS (FAB, glycerol): calcd. for C<sub>36</sub>H<sub>34</sub>NO<sub>8</sub><sup>+</sup> [M+H]<sup>+</sup> *m/z* 608.22789, found *m/z* 608.2310.

Anal. calcd. for C<sub>36</sub>H<sub>33</sub>NO<sub>8</sub> (607.649) C, 71.16; H, 5.47; N, 2.31; found C, 71.03; H, 5.59; N, 2.48%.

### Methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzoyl- $\alpha$ - and $\beta$ -D-galactopyranoside (**10 $\alpha$** and **10 $\beta$** )



Methyl 4,6-*O*-benzylidene-D-galactopyranoside (**9**, 5.00 g, 17.7 mmol)<sup>12</sup> was dissolved in a mixture of dry CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and pyridine (10 mL) then benzoyl chloride (5 mL) was added dropwise to the ice-cooled solution. The reaction mixture was stirred for 4 h at room temperature then ice was added. The cooled mixture was extracted with 0.1 M HCl, then successively washed with satd. NaHCO<sub>3</sub> solution and water, dried (MgSO<sub>4</sub>) and evaporated to dryness. The crude product was dissolved in chloroform and precipitated with hexanes (amorphous foam, 7.80 g, 90%). A small amount was further purified by silica gel column chromatography (hexanes : EtOAc 85:15) and the mixture was separated into anomers.

$\alpha$ -anomer (**10 $\alpha$** ): amorphous foam.

*R<sub>f</sub>* : 0.10, hexanes : EtOAc 7 : 3.

[ $\alpha$ ]<sub>D</sub>: +182 (*c*=0.75, CHCl<sub>3</sub>).

IR (CaF<sub>2</sub>, thin film): 952 (w), 995 (m), 1028 (s), 1071 (m), 1099 (s), 1112 (s), 1181 (m), 1212 (w), 1275 (s), 1317 (m), 1399 (w), 1411 (w), 1452 (m), 1585 (w), 1602 (w), 1727 (s), 2864 (w), 3065 (br w) cm<sup>-1</sup>.



$^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 3.35 (3H, s,  $\text{OCH}_3$ ); 3.79 (1H, s, H-5); 4.03 (1H, d,  $J_{6a,6b} = 12.8$  Hz, H-6a); 4.24 (1H, d,  $J_{6a,6b} = 12.8$  Hz, H-6b); 4.55 (1H, s, H-4); 5.19 (1H, d,  $J_{1,2} = 2.2$  Hz, H-1); 5.48 (1H, s,  $\text{CHPh}$ ); 5.70 (2H, m, H-2 and H-3); 7.14-7.92 (15H, m, arom.).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 55.6 ( $\text{OCH}_3$ ); 62.2 (C-5); 68.8 (C-2); 69.1 (C-6); 69.2 (C-3); 74.2 (C-4); 98.1 (C-1); 100.6 ( $\text{CHPh}$ ); 126.1-133.1 (arom.); 165.9 and 168.1 (CO).

LRMS ( $m/z$ ): 513.1 (100%,  $[\text{M}+\text{Na}^+]$ ).

Anal. calcd. for  $\text{C}_{28}\text{H}_{26}\text{O}_8$  (490.501) C, 68.56; H, 5.34; found C, 68.72; H, 5.25%.

$\beta$ -anomer (**10 $\beta$** ): amorphous foam.

$R_f$ : 0.17, hexanes : EtOAc 7 : 3.

$[\alpha]_D^{25}$ : +165 ( $c=0.7$ ,  $\text{CHCl}_3$ ).

IR ( $\text{CaF}_2$ , thin film): 952 (w), 1013 (m), 1028 (m), 1071 (m), 1082 (m), 1107 (s), 1154 (m), 1176 (m), 1197 (w), 1278 (s), 1315 (m), 1415 (w), 1451 (m), 1601 (w), 1724 (s), 2855 (w), 3064 (br w)  $\text{cm}^{-1}$ .

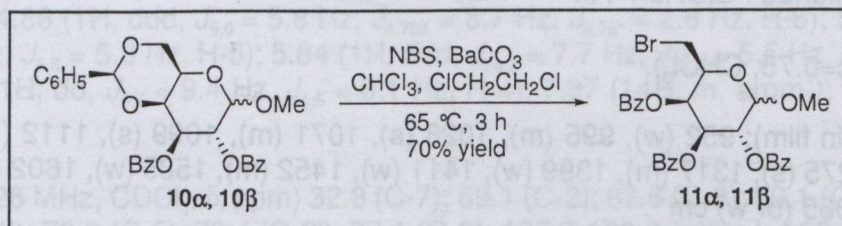
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 3.44 (3H, s,  $\text{OCH}_3$ ); 3.56 (1H, s, H-5); 4.03 (1H, d,  $J_{6a,6b}=12.2$  Hz, H-6a); 4.30 (1H, d,  $J_{6a,6b}=12.2$  Hz, H-6b); 4.49 (1H, d,  $J_{3,4} = 3.8$  Hz, H-4); 4.58 (1H, d,  $J_{1,2} = 8.1$  Hz, H-1); 5.30 (1H, dd,  $J_{2,3} = 10.8$  Hz,  $J_{3,4} = 3.8$  Hz, H-3); 5.45 (1H, s,  $\text{CHPh}$ ); 5.78 (1H, dd,  $J_{1,2} = 8.1$ ,  $J_{2,3} = 10.8$  Hz, H-2); 7.20-7.91 (15H, m, arom.).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 56.5 ( $\text{OCH}_3$ ); 66.4 (C-5); 68.9 (C-6); 69.0 (C-2); 72.7 (C-3); 73.5 (C-4); 100.7 ( $\text{CHPh}$ ); 101.9 (C-1); 126.1-133.3 (arom.); 165.2 and 166.1 (CO).

LRMS ( $m/z$ ): 513.1 (100%,  $[\text{M}+\text{Na}^+]$ ).

Anal. calcd. for  $\text{C}_{28}\text{H}_{26}\text{O}_8$  (490.501) C, 68.56; H, 5.34; found C, 68.43; H, 5.40%.

### Methyl 6-bromo-6-deoxy-2,3,4-tri-*O*-benzoyl- $\alpha$ - and $\beta$ -D-galactopyranoside (**11 $\alpha$** and **11 $\beta$** )





A suspension containing methyl 4,6-benzylidene-2,3-di-*O*-benzoyl-D-galactopyranoside (**10**, 6.60 g, 13.5 mmol), NBS (3.18 g, 17.8 mmol) and barium carbonate (2.80 g, 14.10 mmol) in a mixture of chloroform (165 mL) and 1,2-dichloroethane (25 mL) was stirred under reflux for 3 h. The suspension was filtered and the filtrate was evaporated to dryness. The residue was dissolved in diethyl ether (50 mL), washed with water (3 × 10 mL), dried (MgSO<sub>4</sub>) and evaporated to dryness. The syrup was dissolved in chloroform and precipitated with hexane (amorphous foam, 5.30 g, 70 %). A small amount was further purified by column chromatography (hexanes : EtOAc 9 : 1) and the mixture was separated into anomers.

$\alpha$ -anomer (**11 $\alpha$** ): amorphous foam.

$R_f$ : 0.16, hexanes : EtOAc 9 : 1.

$[\alpha]_D$ : +195 ( $c=0.70$ , CHCl<sub>3</sub>)

IR (CaF<sub>2</sub>, thin film): 974 (w), 1000 (w), 1026 (m), 1068 (s), 1093 (s), 1106 (s), 1177 (w), 1207 (w), 1261 (s), 1283 (s), 1315 (w), 1451 (w), 1601 (w), 1724 (w), 2972 (w), 3059 (w) cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>,  $\delta$ , ppm): 3.39-3.40 (2H, m, H-6a and H-6b); 3.44 (3H, s, OCH<sub>3</sub>); 4.36 (1H, t,  $J_{5,6a} = J_{5,6b} = 6.5$  Hz, H-5); 5.23 (1H, d,  $J_{1,2} = 3.6$  Hz, H-1); 5.57 (1H, dd,  $J_{2,3} = 10.8$ ,  $J_{3,4} = 3.6$  Hz, H-3); 5.87 (1H, dd,  $J_{1,2} = 3.6$  Hz,  $J_{2,3} = 10.8$  Hz, H-2); 5.92 (1H, d,  $J_{3,4} = 3.6$  Hz, H-4); 7.13-8.00 (15H, m, arom.).

<sup>13</sup>C NMR (CDCl<sub>3</sub>,  $\delta$ , ppm): 29.3 (C-6); 55.8 (OCH<sub>3</sub>); 68.4 (C-2); 69.1 (C-3); 69.4 (C-5); 69.8 (C-4); 97.6 (C-1); 128.2-133.6 (arom.); 165.4, 165.5 and 166.0 (CO).

LRMS ( $m/z$ ): 590.9 (100%, [M(<sup>79</sup>Br)+Na<sup>+</sup>]), 592.9 (94, [M(<sup>81</sup>Br)+Na<sup>+</sup>]).

Anal. calcd. for C<sub>28</sub>H<sub>25</sub>BrO<sub>8</sub> (569.397) C, 59.06; H, 4.43; Br, 14.03, found C, 55.87; H, 4.59; Br, 14.35%.

$\beta$ -anomer (**11 $\beta$** ): amorphous foam.

$R_f$ : 0.23, hexanes : EtOAc 9 : 1.

$[\alpha]_D$ : +79 ( $c=0.75$ , CHCl<sub>3</sub>).

IR (CaF<sub>2</sub>, thin film): 953 (w), 1027 (m), 1046 (m), 1069 (m), 1097 (s), 1105 (s), 1124 (m), 1177 (w), 1280 (s), 1270 (s), 1315 (w), 1451 (w), 1601 (w), 1724 (s), 2966 (br w), 3062 (br w) cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>,  $\delta$ , ppm): 3.42-3.49 (2H, m, H-6a and H-6b); 3.55 (3H, s, OCH<sub>3</sub>); 4.10 (1H,



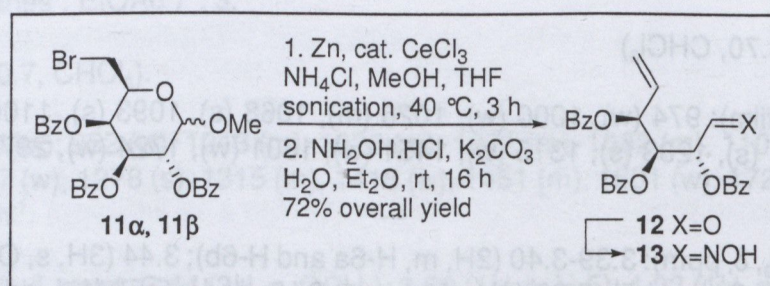
t,  $J_{5,6a} = J_{5,6b} = 6.9$  Hz, H-5); 4.66 (1H, d,  $J_{1,2} = 7.9$  Hz, H-1); 5.50 (1H, dd,  $J_{2,3} = 10.3$  Hz,  $J_{3,4} = 3.2$  Hz, H-3); 5.68 (1H, dd,  $J_{1,2} = 7.9$  Hz,  $J_{2,3} = 10.3$  Hz, H-2); 5.94 (1H, d,  $J_{3,4} = 3.2$  Hz, H-4); 7.15-8.0 (15H, m, arom.).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 28.5 (C-6); 57.3 ( $\text{OCH}_3$ ); 68.6 (C-4); 69.5 (C-2); 71.7 (C-3); 74.0 (C-5); 102.3 (C-1); 128.3-133.6 (arom.); 165.3 and 165.4 (CO).

LRMS ( $m/z$ ): 590.9 (100%,  $[\text{M}(^{79}\text{Br})+\text{Na}^+]$ ), 593.0 (95,  $[\text{M}(^{81}\text{Br})+\text{Na}^+]$ ).

Anal. calcd. for  $\text{C}_{28}\text{H}_{25}\text{BrO}_8$  (569.397) C, 59.06; H, 4.43; Br, 14.03, found C, 55.95; H, 4.64; Br, 14.24%.

### 2,3,4-Tri-*O*-benzoyl-5,6-dideoxy-L-arabino-hex-5-enoate oxime (13)



A suspension of zinc dust (5.20 g, 93.2 mmol),  $\text{NH}_4\text{Cl}$  (8.80 g, 93.20 mmol) and a catalytical amount of  $\text{CeCl}_3$ <sup>11</sup> were sonicated in a mixture of MeOH (50 mL) and THF (70 mL) for 15 min. After this pretreatment period methyl 6-bromo-6-deoxy-2,3,4-tri-*O*-benzoyl-D-galactopyranoside (**11**, 5.20 g, 9.3 mmol) was added to the reaction mixture. After 3 h sonication at  $40^\circ\text{C}$  the reaction was complete, the suspension was filtered, and evaporated to dryness. The residue was dissolved in  $\text{Et}_2\text{O}$  (30 mL), extracted with water ( $3 \times 10$  mL) and dried ( $\text{MgSO}_4$ ). The crude aldehyde **12** was used without further purification in the following reaction. The mixture of the above ethereal solution and water (30 mL) was cooled in an ice bath and  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (4.44 g, 93.00 mmol) was added. A solution of  $\text{K}_2\text{CO}_3$  (10.20 g, 93.0 mmol) in water (20 mL) was added dropwise to the reaction mixture and stirred for 16 h. The organic layer was separated, washed with water ( $2 \times 5$  mL), dried ( $\text{MgSO}_4$ ) and concentrated. The residue was subjected to column chromatography (hexanes: EtOAc 85:15) to yield a sirupy product (3.20 g, 72 %,  $E:Z = 2:1$ , based on the integral intensities of proton H-6a in the  $^1\text{H}$  NMR spectrum of the isomer mixture).

$R_f$ : 0.18, 0.23 ( $E/Z$ ), hexanes : EtOAc 8 : 2.

IR ( $\text{CaF}_2$ , thin film): 943 (w), 1026 (m), 1069 (m), 1096 (s), 1107 (m), 1263 (s), 1107 (s), 1177 (w), 1263 (s), 1316 (m), 1451 (m), 1584 (w), 1601 (w), 1724 (s), 2931 (w), 3063 (w), 3434 (br w)  $\text{cm}^{-1}$ .



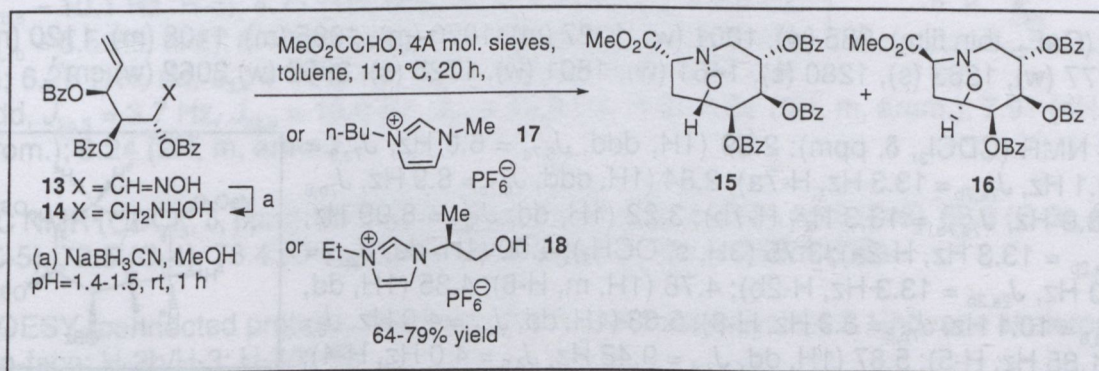
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 5.34 (0.33 H, d,  $J_{5,6a} = 11.1$  Hz, H-6a); 5.40 (0.67 H, d,  $J_{5,6a} = 10.1$  Hz, H-6a); (1H, d,  $J_{6a,6b} = 17.1$  Hz, H-6b) 6.00 (4H, m, H-2, H-3, H-4 and H-5); 7.46 (10 H, m, H-1, arom.); 8.03 (6 H, m, arom.).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 66.1 (C-2<sub>Z</sub>); 69.6 (C-2<sub>E</sub>); 72.2 (C-4<sub>Z</sub>); 72.9 (C-4<sub>E</sub>); 73.1 (C-3<sub>Z</sub>); 73.3 (C-3<sub>E</sub>); 120.6 (C-6<sub>Z</sub>); 121.1 (C-6<sub>E</sub>); 128.3-133.4 (arom.); 131.2 (C-5<sub>E</sub>); 131.7 (C-5<sub>Z</sub>); 145.8 (C-1<sub>E</sub>); 147.0 (C-1<sub>Z</sub>); 165.1 and 165.5 (CO).

LRMS ( $m/z$ ): 474.0 (50%,  $[\text{M}+\text{H}]^+$ ), 496.1 (63,  $[\text{M}+\text{Na}]^+$ ).

Anal. calcd. for  $\text{C}_{27}\text{H}_{23}\text{NO}_7$  (473.474) C, 68.49; H, 4.90; N, 2.96; found C, 68.30; H, 5.18; N, 3.20%.

**(3*S*,4*R*,5*R*,6*S*,8*R*)-8-(Methoxycarbonyl)-9-oxa-1-aza-bicyclo[4.2.1]nonane-3,4,5-triyl tribenzoate (15) and (3*S*,4*R*,5*R*,6*R*,8*S*)-8-(methoxy-carbonyl)-9-oxa-1-aza-bicyclo[4.2.1]nonane-3,4,5-triyl tribenzoate (16)**



To a stirred solution of oxime **13** (0.300 g, 0.63 mmol) in MeOH (100 mL) was added  $\text{NaBH}_3\text{CN}$  (0.240 g, 3.79 mmol, 6 equiv.). The pH of the solution was maintained between 1.4-1.5 with 1 M HCl/MeOH and monitored either by a combined pH glass electrode for organic solutions or by the indicator bromocresol green. After 1 h the solution was evaporated *in vacuo* (the pH of the reaction mixture did not change further), co-evaporated to dryness with toluene ( $3 \times 20$  mL). The residue was dissolved in  $\text{Et}_2\text{O}$  (100 mL) and the ethereal solution was washed with aq. 0.1 M HCl (20 mL), satd. aq.  $\text{Na}_2\text{CO}_3$  solution ( $2 \times 50$  mL) and distilled water ( $3 \times 50$  mL), dried ( $\text{MgSO}_4$ ) and evaporated to dryness *in vacuo*. The obtained hydroxylamine **14** was used without any further purification.  $R_f$ : 0.35, hexanes : EtOAc 1 : 1; TLC-MS ( $m/z$ ): 476 (100%,  $[\text{M}+\text{H}]^+$ ), 498 (12,  $[\text{M}+\text{Na}]^+$ ).

The above crude product was dissolved in dry toluene (100 mL) and treated with freshly prepared methyl glyoxylate<sup>13</sup> (0.140 g, 1.57 mmol, 2.5 equiv.) in the presence of 4 Å molecular sieves. After stirring at 110 °C for 16 h, the solution was filtered, evaporated *in vacuo* and co-evaporated with toluene ( $3 \times 50$  mL). The residue was purified by column chromatography (hexanes : EtOAc 85 : 15). The diastereoisomers were separated in an



additional run of silica gel column chromatography (hexanes : *i*-PrOH 10 : 0.5) to give the cycloaddition product **15** (0.165 g) and **16** (0.055 g) in 64 % overall yield in a ratio of 3 : 1. In another experiment, starting from oxime **13** (0.120 g, 0.25 mmol), the cycloaddition step was carried out in achiral ionic solvent 1-*n*-butyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate **17** and the reaction yielded diastereoisomers **15** (0.088 g) and **16** (0.011 g) in 72 % overall yield in a ratio of 8 : 1.

When the same reaction sequence was repeated with **13** (0.100 g, 0.21 mmol,) in chiral ionic solvent (*S*)-3-ethyl-1-(1-hydroxypropan-2-yl)-1*H*-imidazol-3-ium hexafluorophosphate **18**<sup>1</sup> diastereoisomer **15** (0.088 g) was obtained in 79 % overall yield. In the <sup>1</sup>H NMR spectrum of this sample there were only very small signals, beyond the signals of **15**, originating from unidentified impurities.

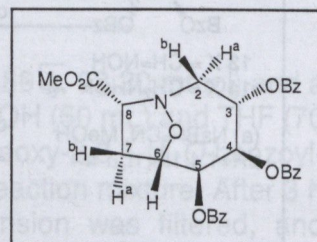
### Compound 15:

*R*<sub>f</sub>: 0.20, hexanes : EtOAc 7 : 3.

[α]<sub>D</sub>: +170 (c=0.55, CHCl<sub>3</sub>).

IR (CaF<sub>2</sub>, thin film): 985 (w), 1001 (w), 1027 (m), 1070 (m), 1095 (m), 1108 (m), 1120 (m), 1177 (w), 1263 (s), 1280 (s), 1451 (w), 1601 (w), 1725 (s), 2952 (w) 3062 (w) cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, δ, ppm): 2.69 (1H, ddd, *J*<sub>6,7a</sub> = 6.0 Hz, *J*<sub>7a,8</sub> = 10.1 Hz, *J*<sub>7a,7b</sub> = 13.3 Hz, H-7a); 2.84 (1H, ddd, *J*<sub>6,7b</sub> = 8.9 Hz, *J*<sub>7b,8</sub> = 8.9 Hz, *J*<sub>7a,7b</sub> = 13.3 Hz, H-7b); 3.22 (1H, dd, *J*<sub>2a,3</sub> = 8.99 Hz, *J*<sub>2a,2b</sub> = 13.3 Hz, H-2a); 3.75 (3H, s, OCH<sub>3</sub>); 4.00 (1H, dd, *J*<sub>2b,3</sub> = 4.0 Hz, *J*<sub>2a,2b</sub> = 13.3 Hz, H-2b); 4.76 (1H, m, H-6); 4.35 (1H, dd, *J*<sub>7a,8</sub> = 10.1 Hz, *J*<sub>7b,8</sub> = 8.9 Hz, H-8); 5.68 (1H, dd, *J*<sub>4,5</sub> = 4.0 Hz, *J*<sub>5,6</sub> = 1.85 Hz, H-5); 5.87 (1H, dd, *J*<sub>3,4</sub> = 9.48 Hz, *J*<sub>4,5</sub> = 4.0 Hz, H-4); 6.15 (1H, ddd, *J*<sub>2a,3</sub> = 8.99 Hz, *J*<sub>2b,3</sub> = 4.0 Hz, *J*<sub>3,4</sub> = 9.48 Hz, H-3); 7.17-8.10 (15H, m, arom. CH).



<sup>13</sup>C NMR (CDCl<sub>3</sub>, δ, ppm): 32.9 (C-7); 52.6 (OCH<sub>3</sub>); 54.1 (C-2); 67.1 (C-3); 68.2 (C-8); 72.0 (C-5); 72.1 (C-4); 81.2 (C-6); 128.2-133.4 (arom.); 165.0, 165.4, 165.8 (3 × benzoyl CO); 168.1 (acetyl CO).

NOESY (connected protons, relative to the 9-oxa-1-azabicyclo[4.2.1]nonane skeleton)

top-face: H-2b/H-3; H-6/H-7b/H-8

bottom-face: H-2a/H-4/H-5/H-7a.

LRMS (*m/z*): 546.3 (100%, [M+H]<sup>+</sup>), 568.2 (37, [M+Na]<sup>+</sup>).

HRMS (FAB, glycerol): calcd. for C<sub>30</sub>H<sub>28</sub>NO<sub>9</sub><sup>+</sup> [M+H]<sup>+</sup> *m/z* 546.17586, found *m/z* 546.17794.

Anal. calcd. for C<sub>30</sub>H<sub>27</sub>NO<sub>9</sub> (545.537) C, 66.05; H, 4.99; N, 2.57; found C, 65.87; H, 5.18;



N, 2.73%.

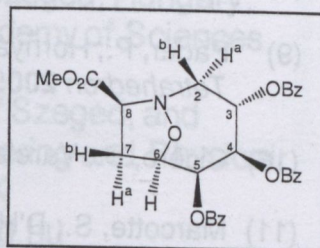
### Compound 16:

$R_f$ : 0.26, hexanes : EtOAc 7 : 3.

$[\alpha]_D$ : +7 ( $c=0.5$ ,  $\text{CHCl}_3$ ).

IR ( $\text{CaF}_2$ , thin film): 944 (w), 1026 (m), 1069 (m), 1096 (s), 1120 (s), 1178 (m), 1219 (m), 1265 (s), 1316 (m), 1451 (m), 1470 (m), 1585 (w), 1602 (w), 1730 (s), 2849 (s), 2916 (s), 3062 (w), 3259 (br w)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ ,  $\delta$ , ppm) 2.11 (1H, ddd,  $J_{6,7a} = 9.6$  Hz,  $J_{7a,7b} = 13.7$  Hz,  $J_{7a,8} = 9.3$  Hz, H-7a); 3.21 (1H, ddd,  $J_{6,7b} = 5.5$  Hz,  $J_{7b,7a} = 13.7$  Hz,  $J_{7b,8} = 10.1$  Hz, H-7b); 3.34 (3H, s, Me); 3.64 (1H, dd,  $J_{2a,2b} = 15.0$  Hz,  $J_{2b,3} = 3.7$  Hz, H-2b); 3.72 (1H, dd,  $J_{2a,2b} = 15.0$  Hz,  $J_{2a,3} = 10.0$  Hz, H-2a); 4.09 (1H, dd,  $J_{7a,8} = 9.3$  Hz,  $J_{7b,8} = 10.1$  Hz, H-8); 4.71 (1H, ddd,  $J_{5,6} = 7.9$  Hz,  $J_{6,7a} = 9.6$  Hz,  $J_{6,7b} = 5.5$  Hz, H-6); 6.10 (1H, dd,  $J_{4,5} = 4.9$  Hz,  $J_{5,6} = 7.9$  Hz, H-5); 6.25 (1H, dd,  $J_{3,4} = 10.2$  Hz,  $J_{4,5} = 4.9$  Hz, H-4); 6.30 (1H, ddd,  $J_{2b,3} = 3.7$  Hz,  $J_{2a,3} = 10.0$  Hz,  $J_{3,4} = 10.2$  Hz, H-3); 6.92 (9H, m, arom.); 7.91 (4H, m, arom.); 8.24 (2H, m, arom.).



$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 35.0 (C-7), 53.3 ( $\text{OCH}_3$ ), 56.2 (C-2), 66.6 (C-8), 68.8 (C-3), 69.7 (C-5), 72.5 (C-4), 78.4 (C-6), 128.5-133.9 (arom.), 165.5, 168.6 (CO).

NOESY (connected protons, relative to the 9-oxa-1-azabicyclo[4.2.1]nonane skeleton)  
top-face: H-2b/H-3; H-3/H-7b

bottom-face: H-2a/H-4; H-4/H-5/H-6; H-5/H-6/H-7a; H-7a/H-8.

LRMS ( $m/z$ ): 546.1 (100%,  $[\text{M}+\text{H}^+]$ ), 568.1 (39,  $[\text{M}+\text{Na}^+]$ ).

HRMS (FAB, glycerol): calcd. for  $\text{C}_{30}\text{H}_{28}\text{NO}_9$   $[\text{M}+\text{H}]^+$   $m/z$  546.17586, found  $m/z$  546.17821.

Anal. calcd. for  $\text{C}_{30}\text{H}_{27}\text{NO}_9$  (545.537) C, 66.05; H, 4.99; N, 2.57; found C, 66.19; H, 5.21; N, 2.78%.

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**Single diastereomers of polyhydroxylated 9-oxa-1-azabicyclo[4.2.1]nonanes from intramolecular 1,3-dipolar cycloaddition of  $\omega$ -unsaturated nitrones**

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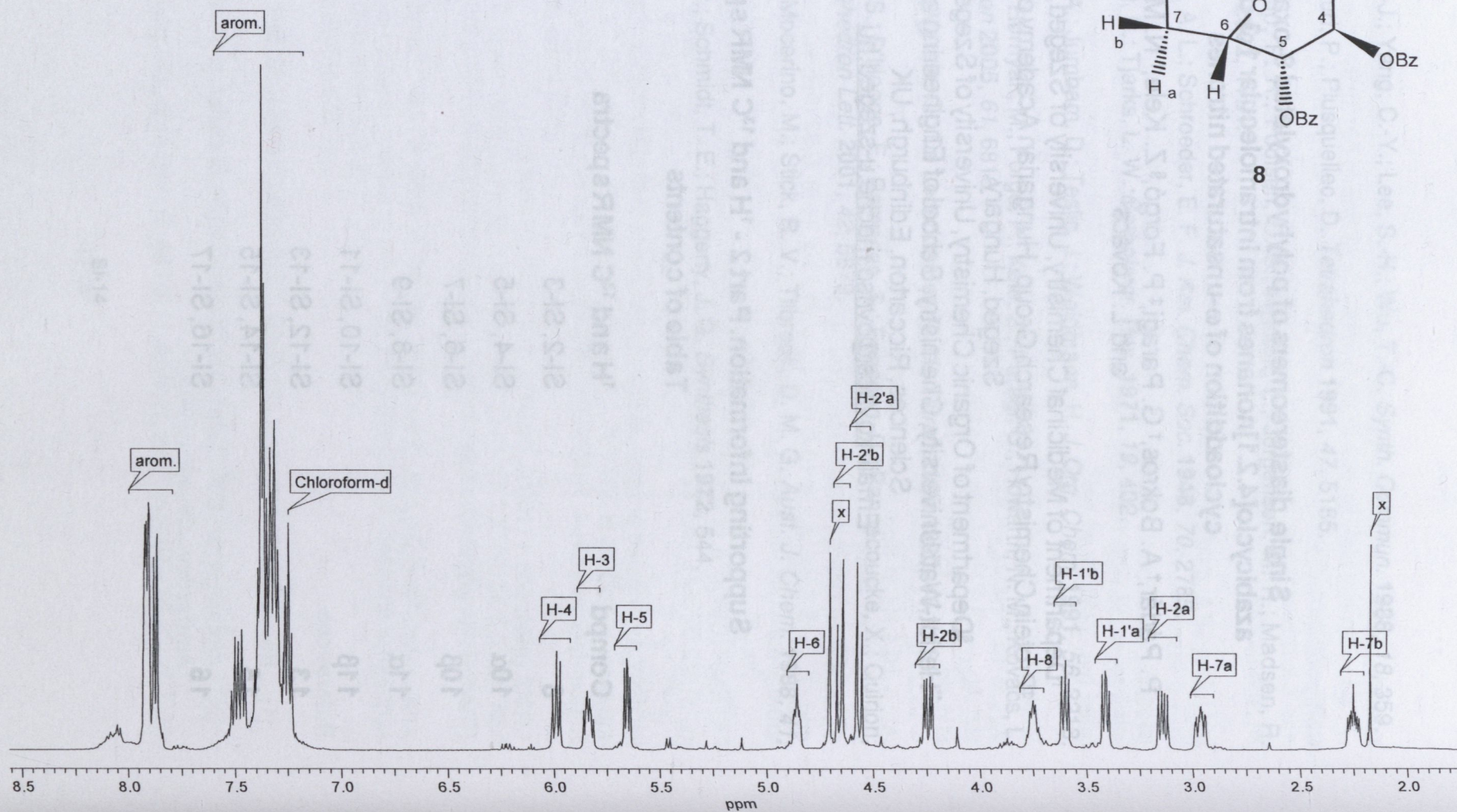
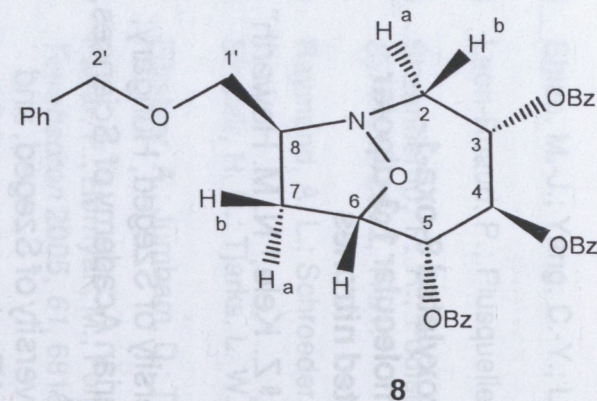
**Supporting Information. Part 2 - <sup>1</sup>H and <sup>13</sup>C NMR spectra**

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11 $\alpha$	SI-8, SI-9
11 $\beta$	SI-10, SI-11
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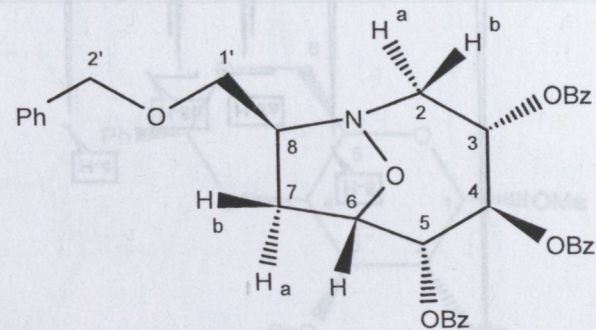


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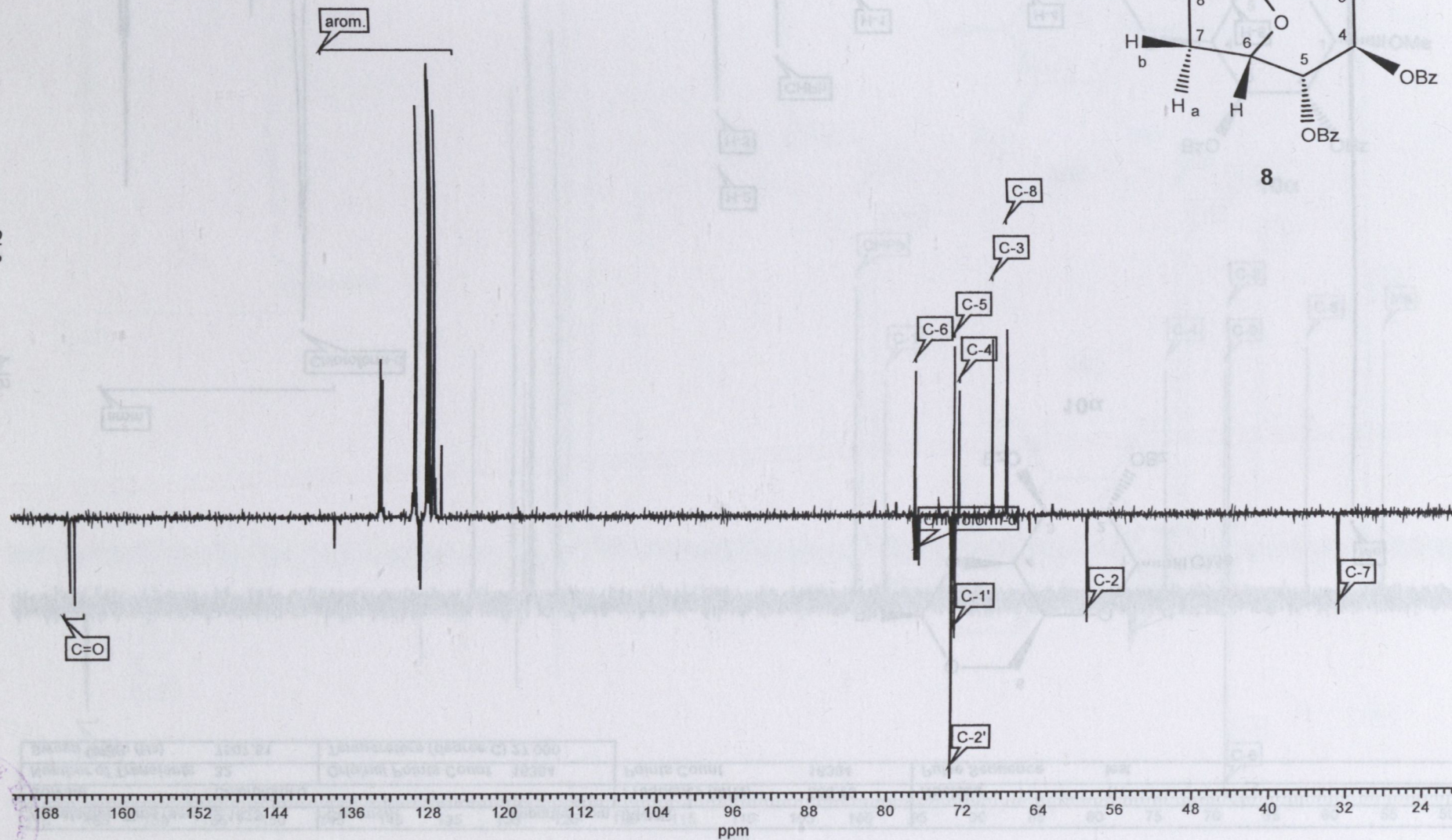


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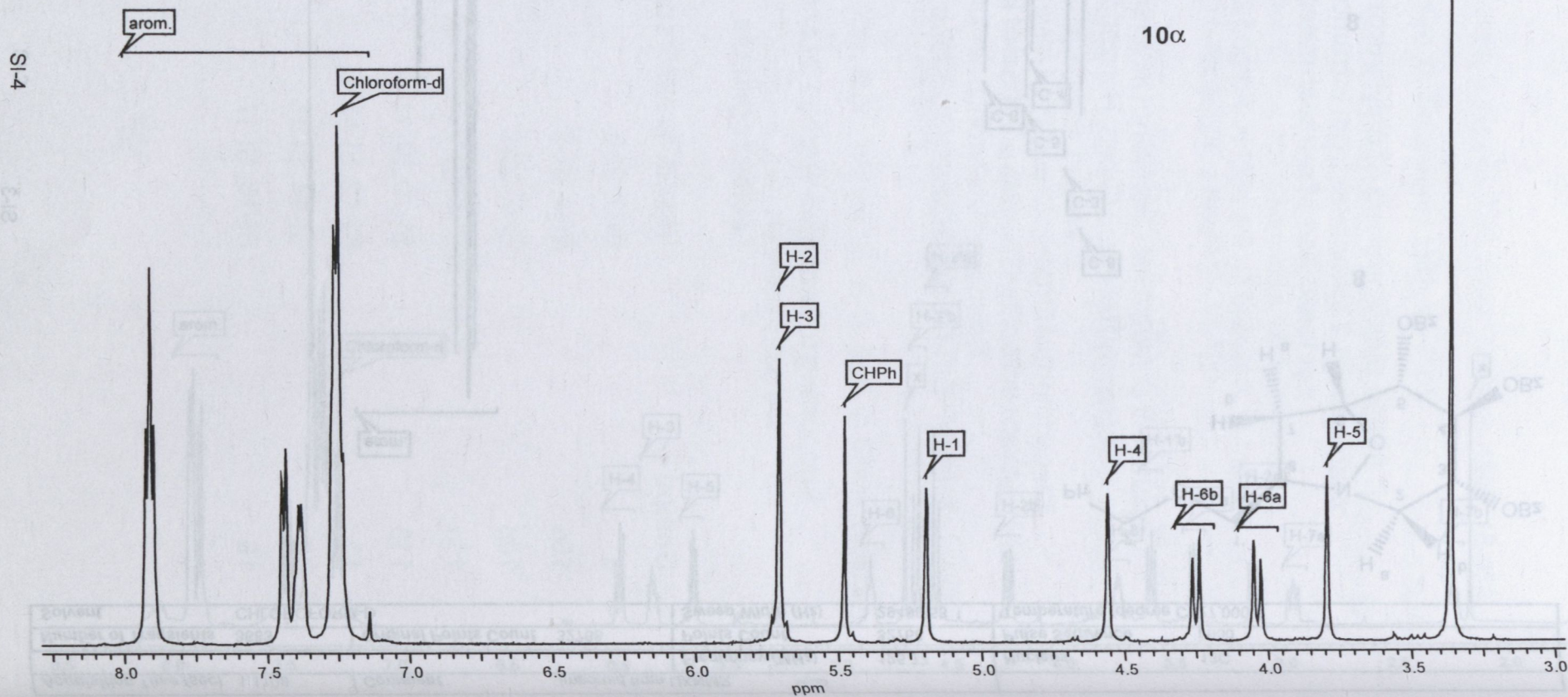
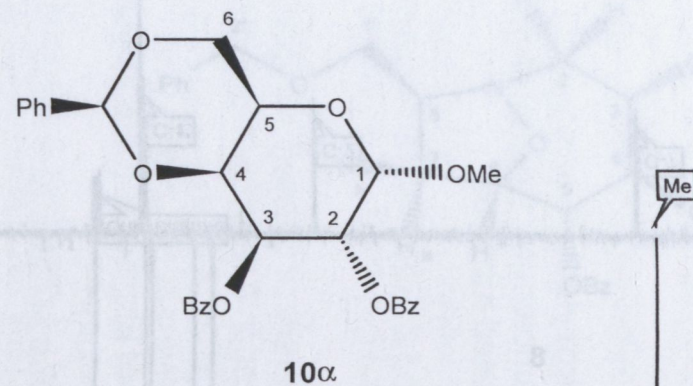
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S1-3





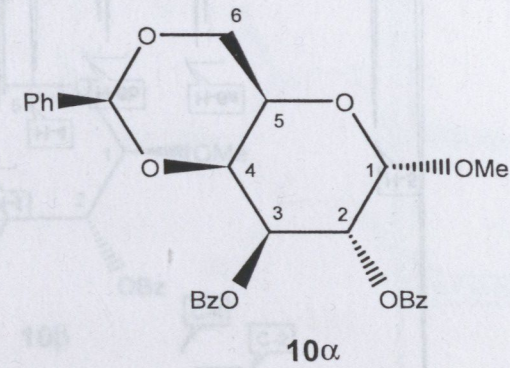
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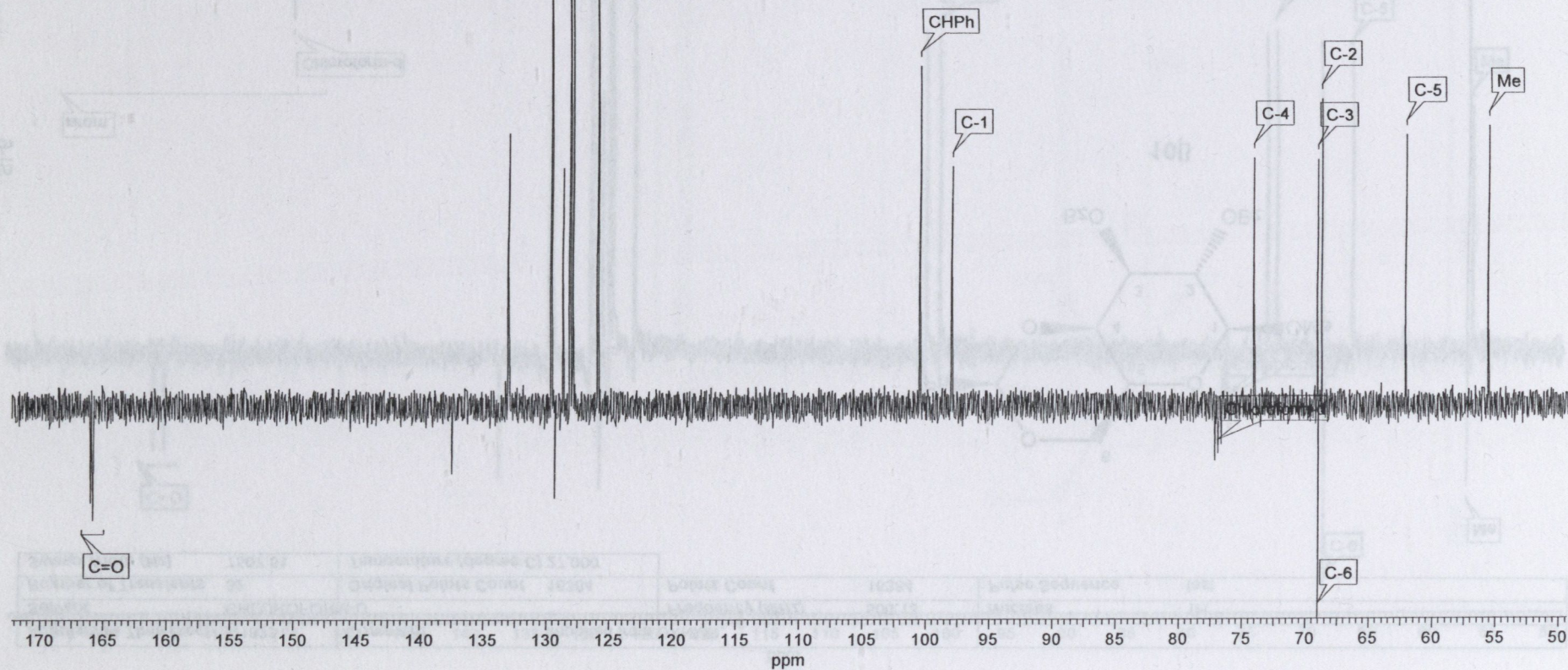


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				Nucleus	<sup>13</sup> C
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				Temperature (degree C)	27.000

arom.

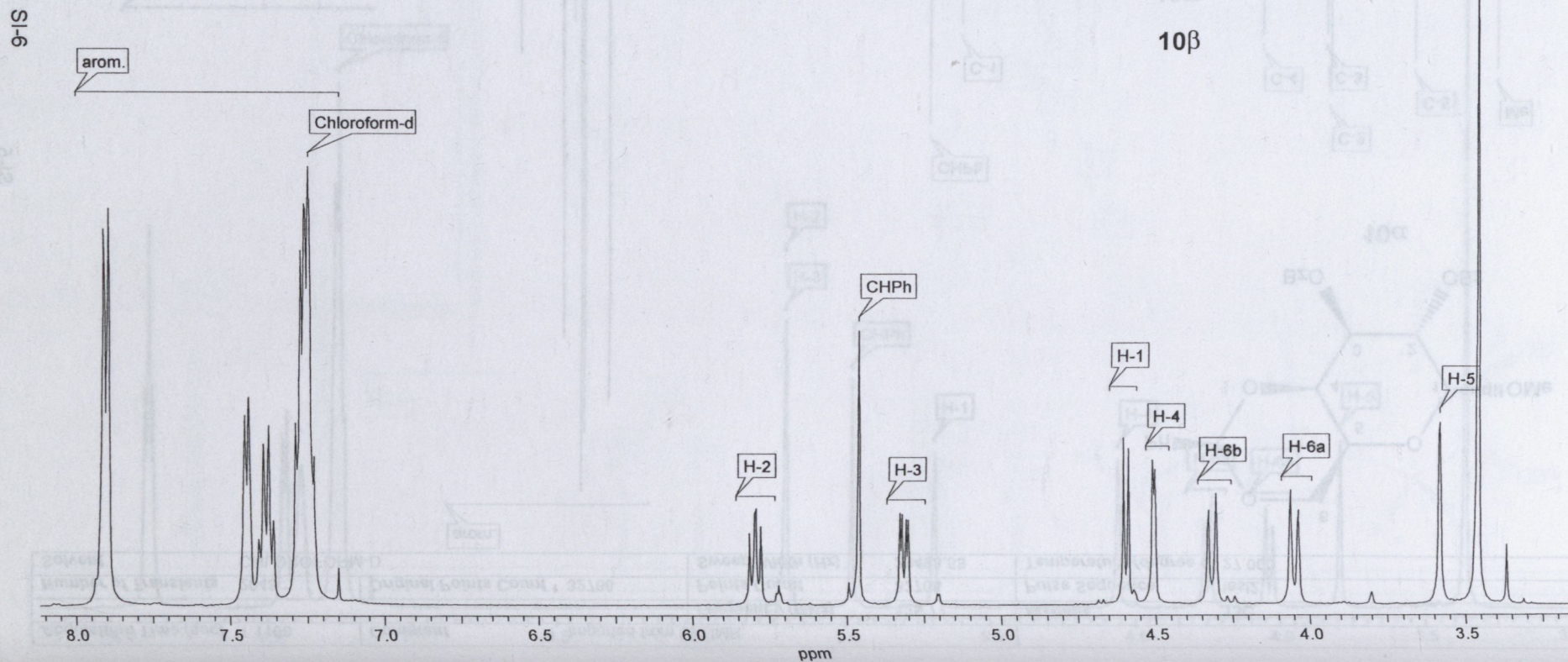
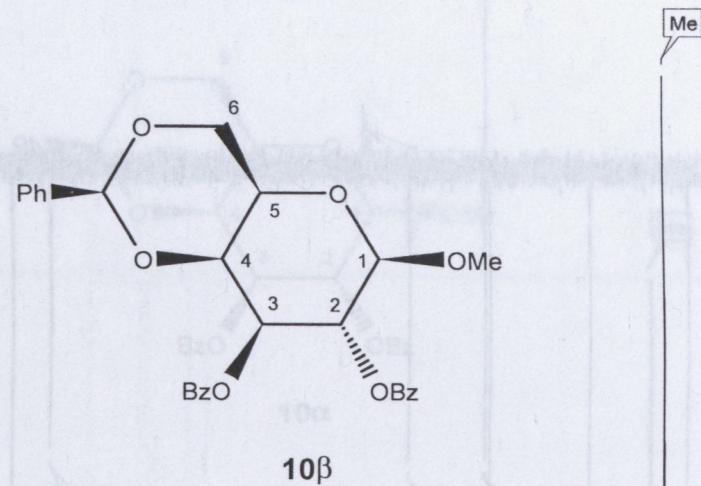


S-5





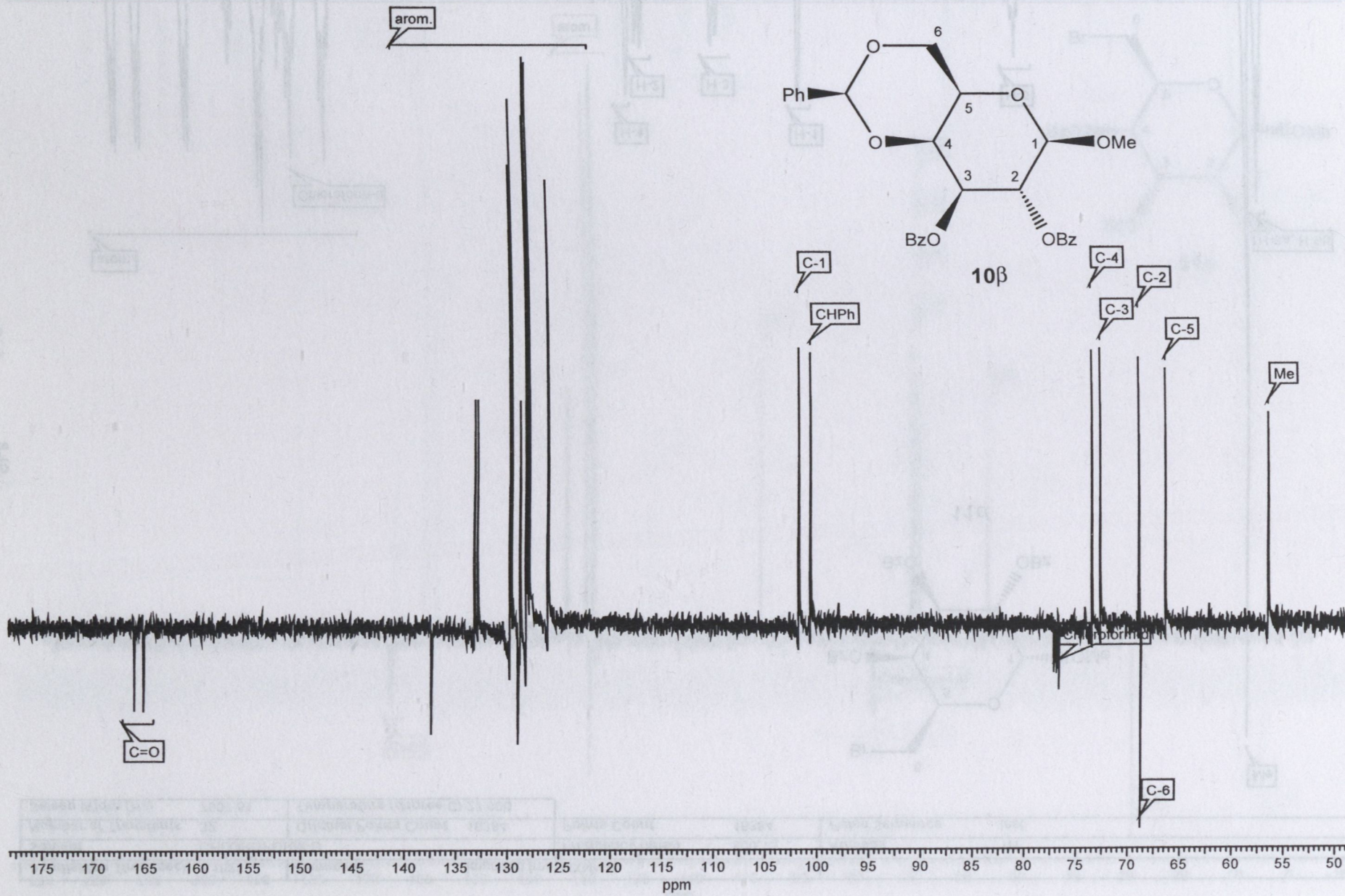
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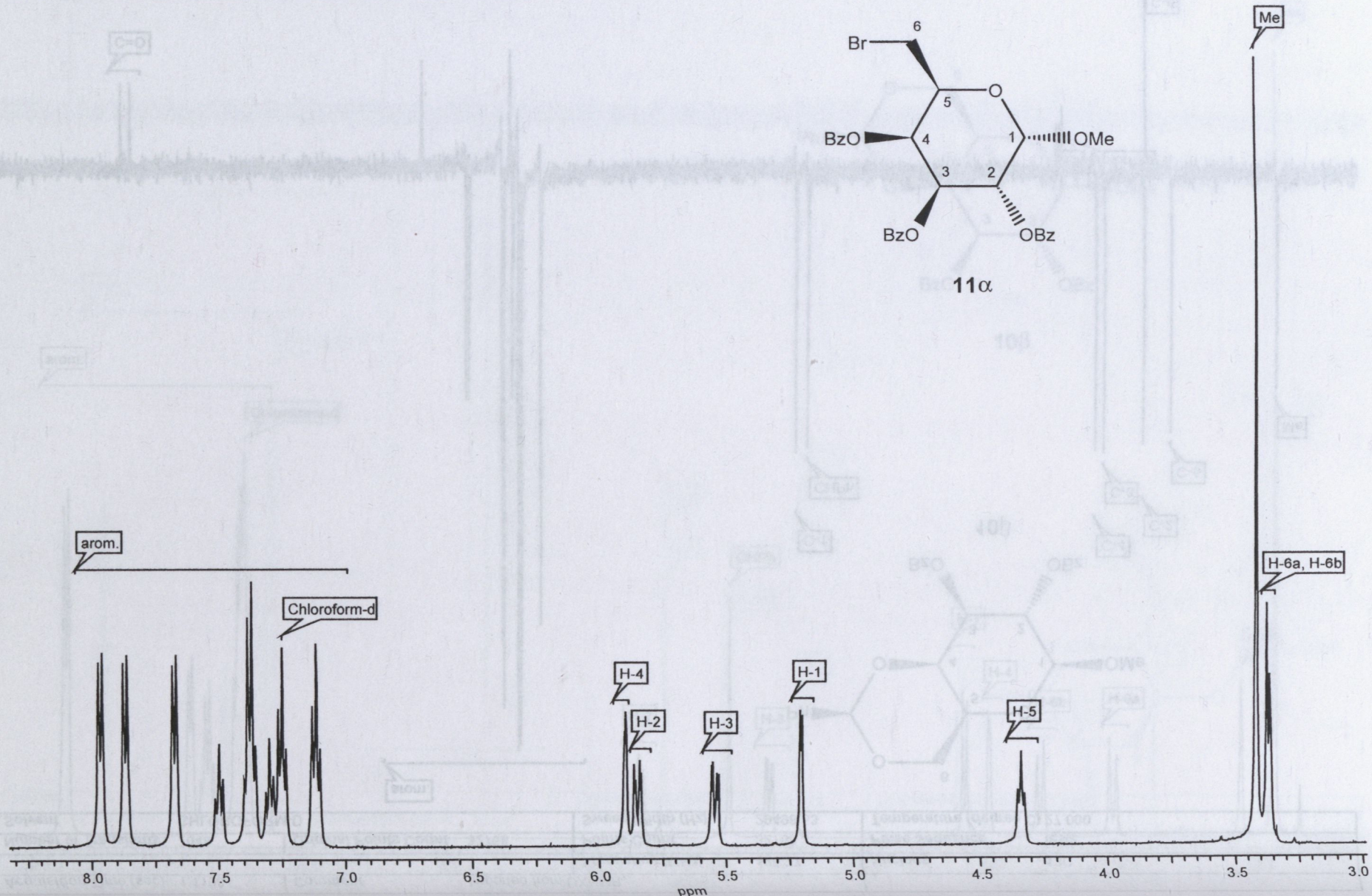
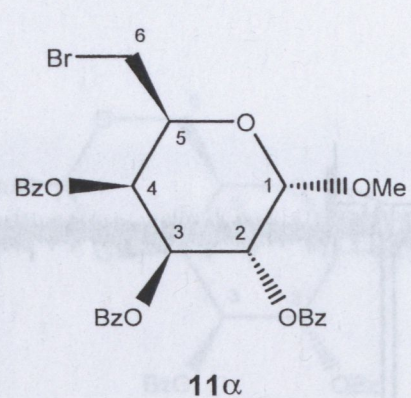
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SI-7





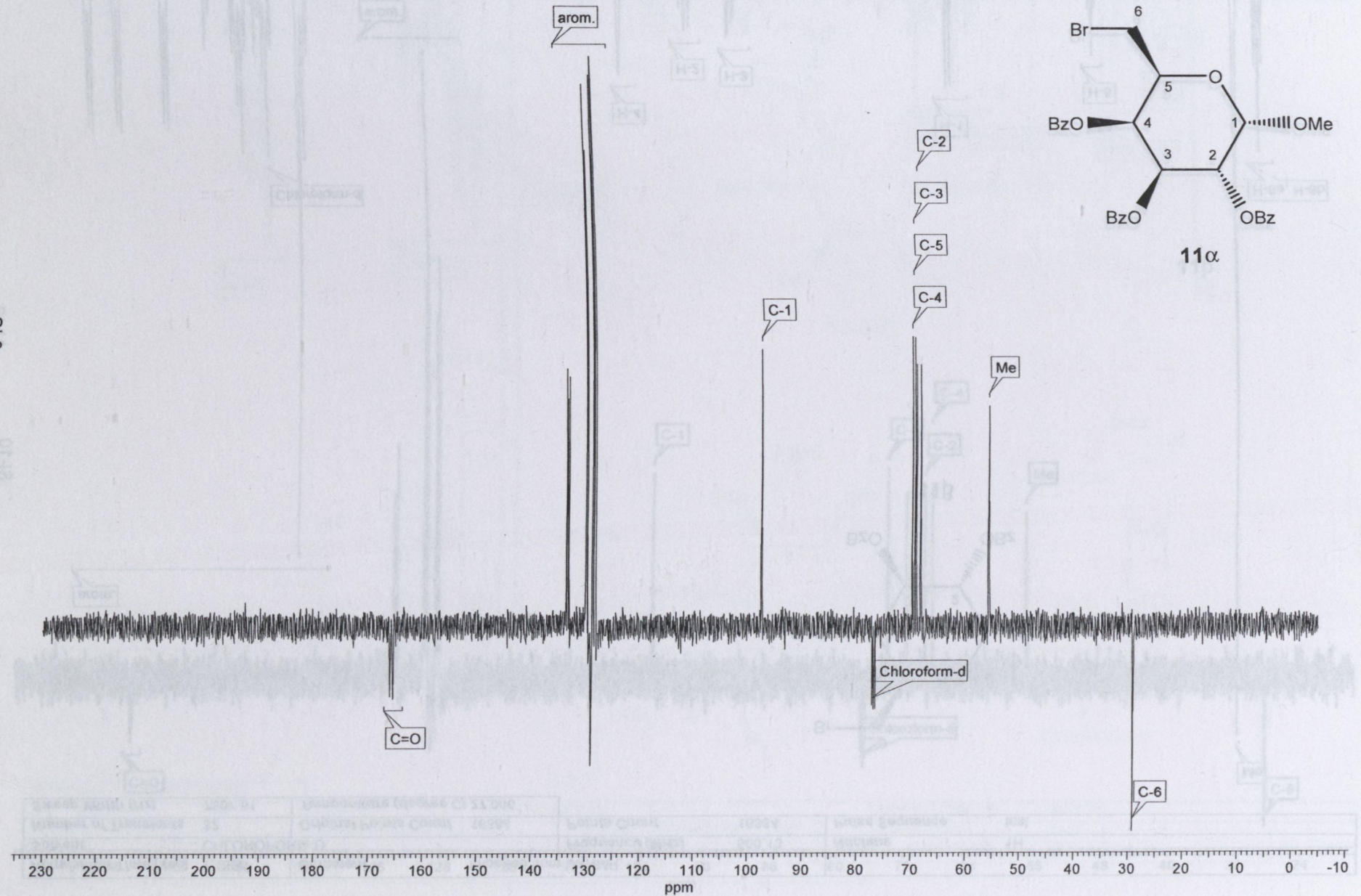
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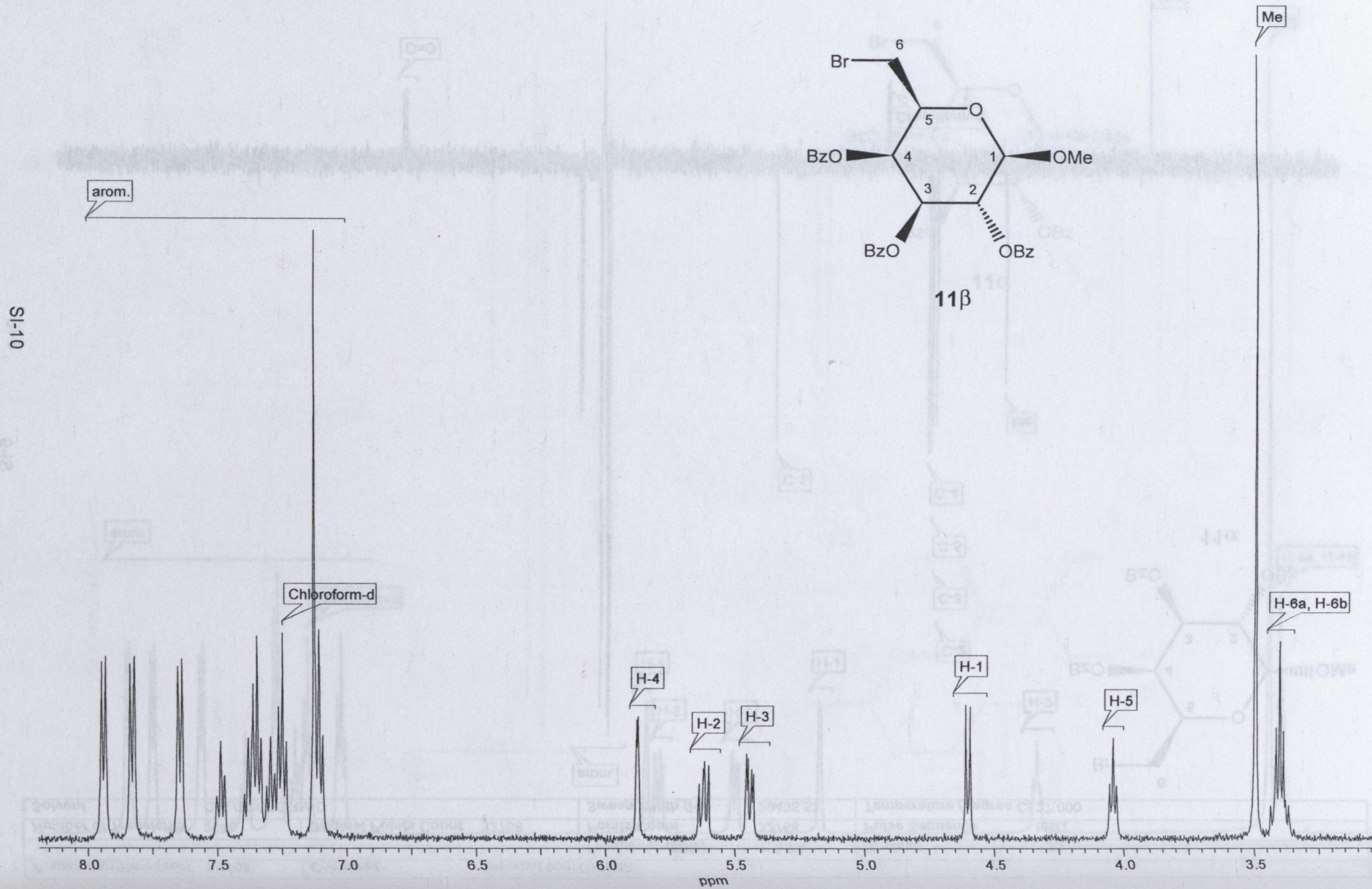
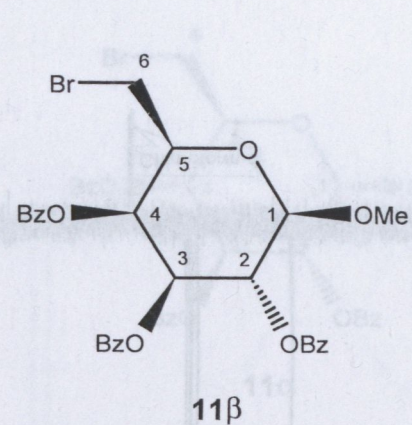
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61S



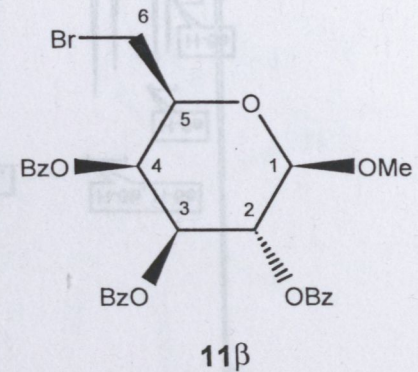


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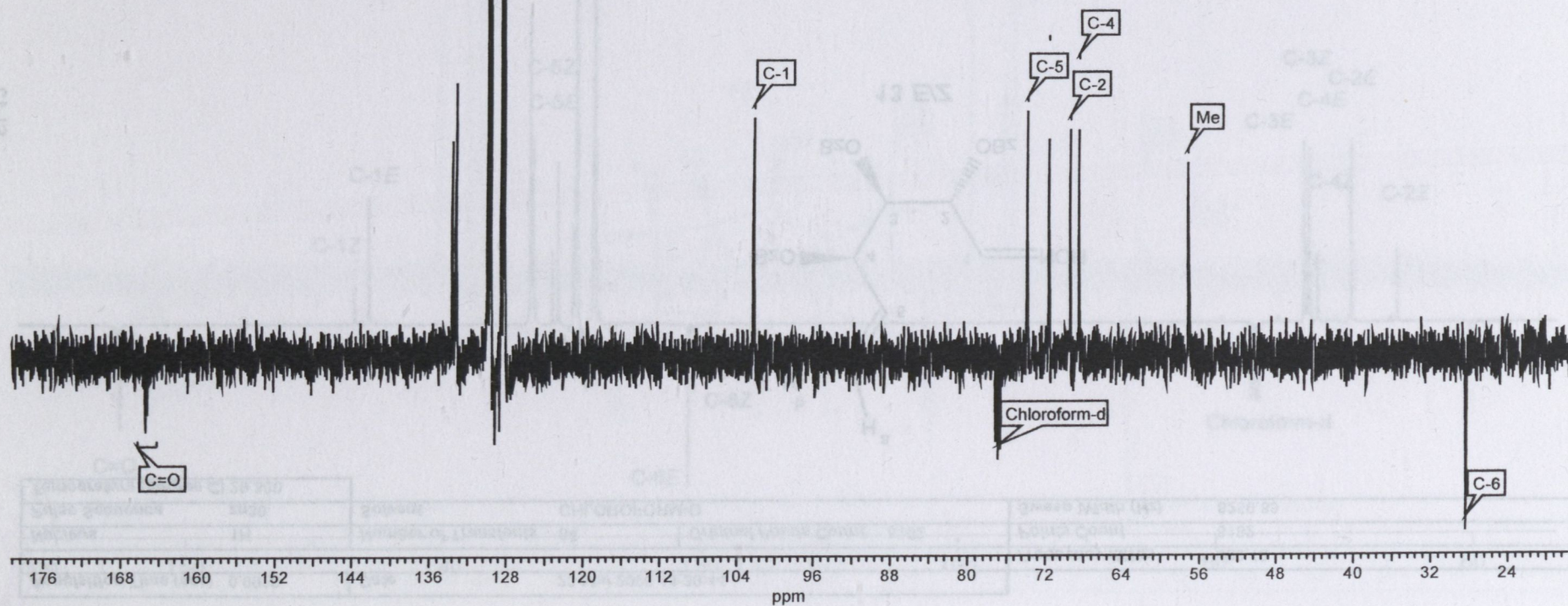




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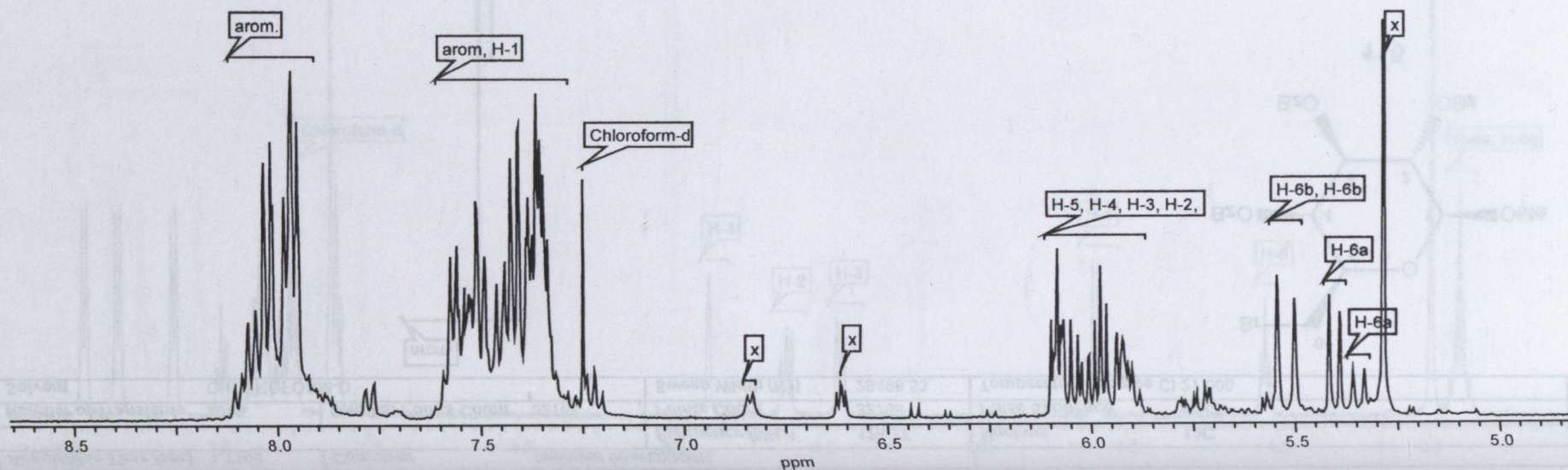
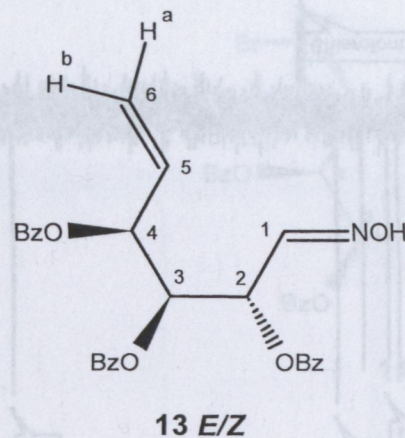


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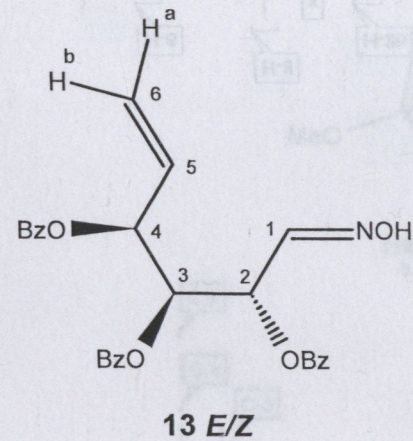


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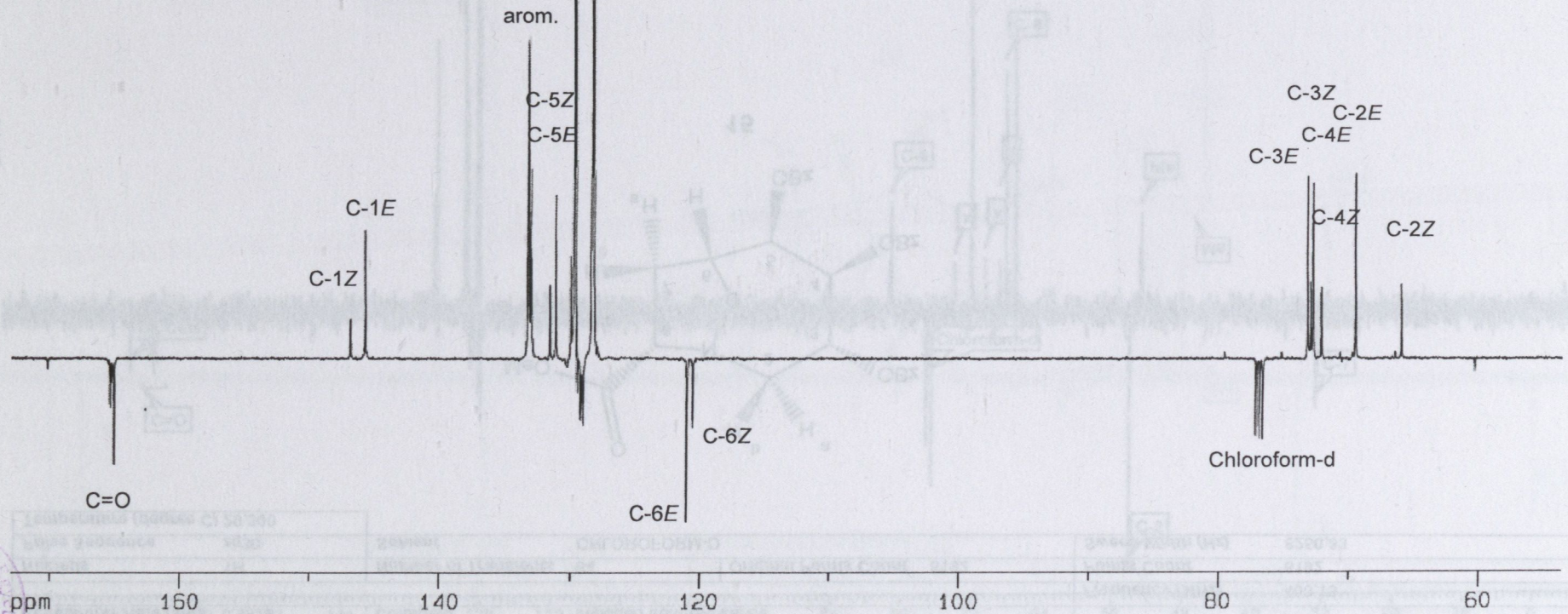




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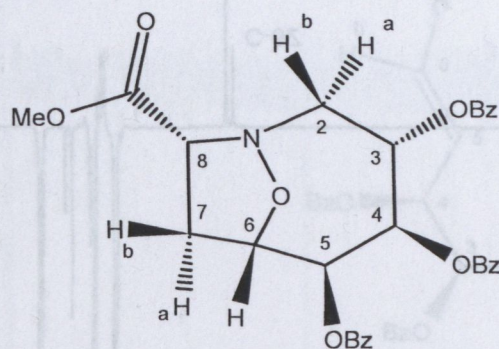


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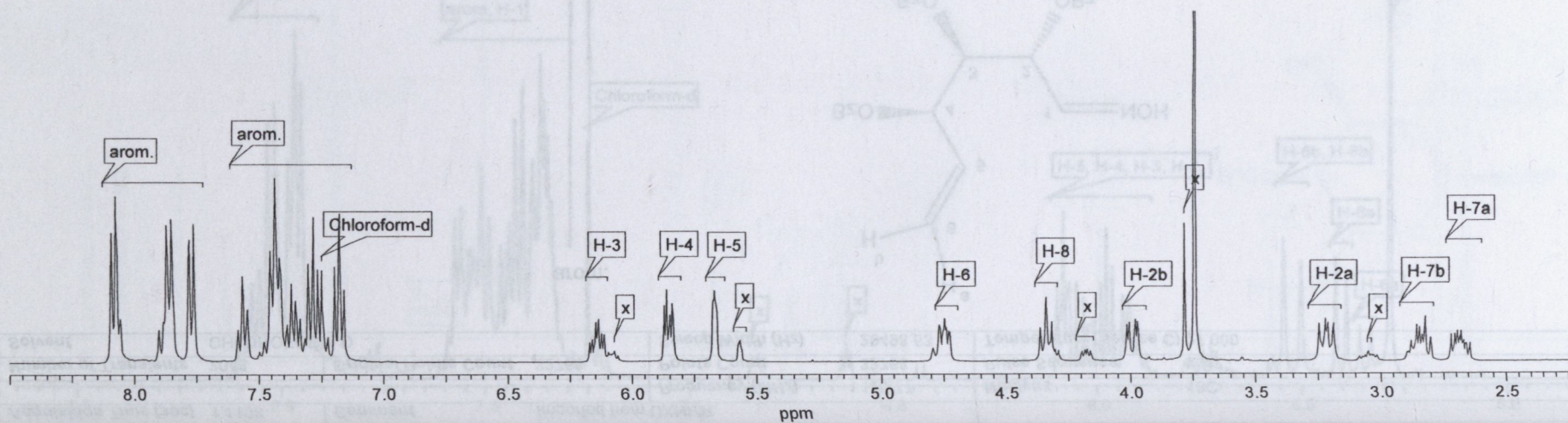




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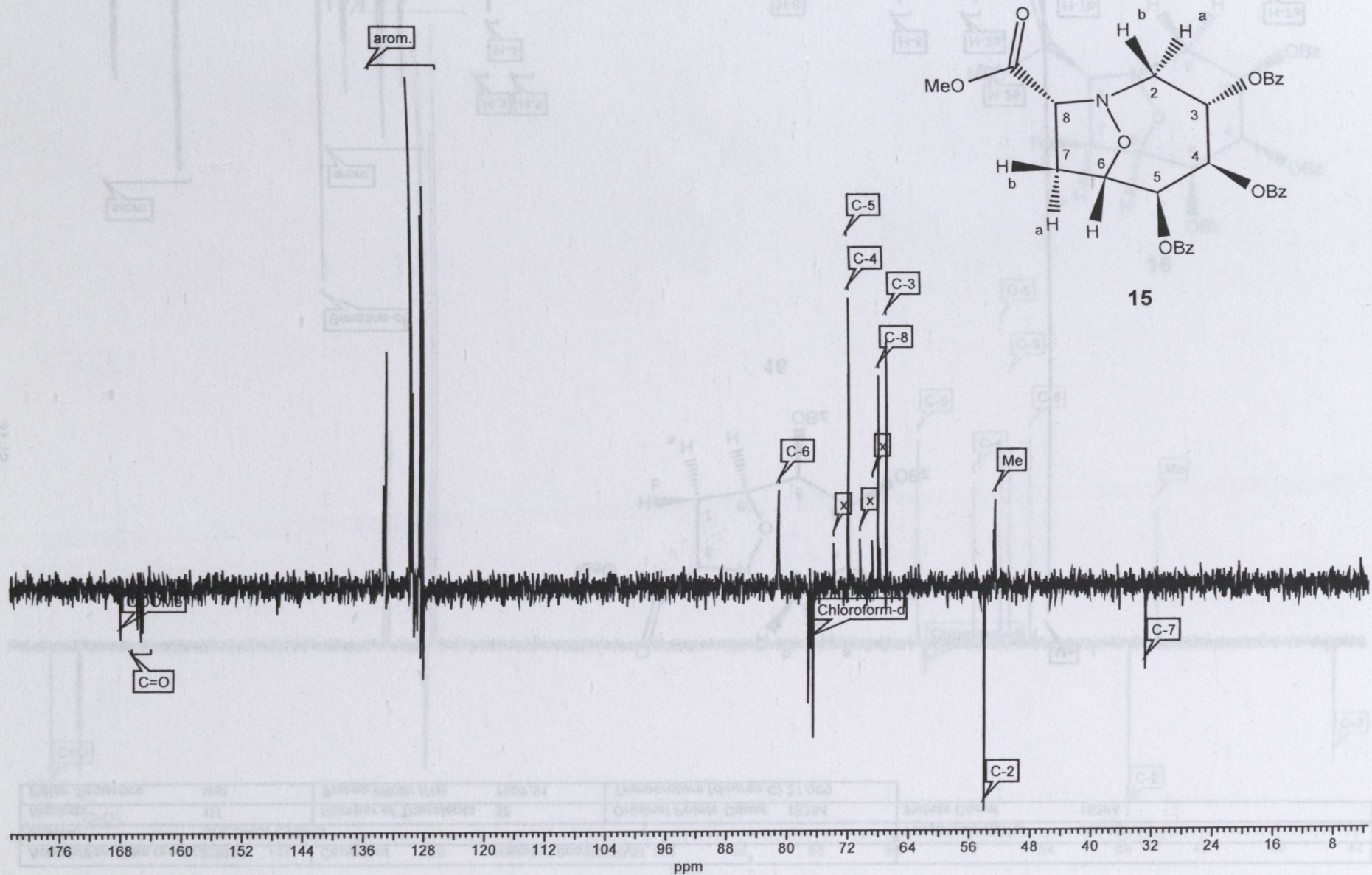
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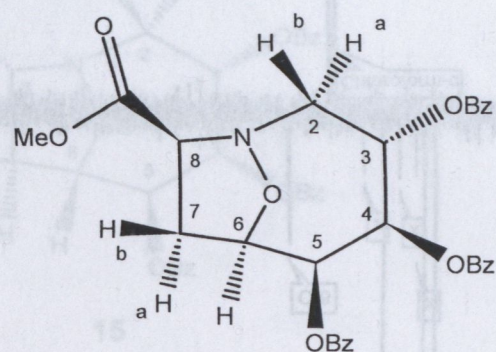
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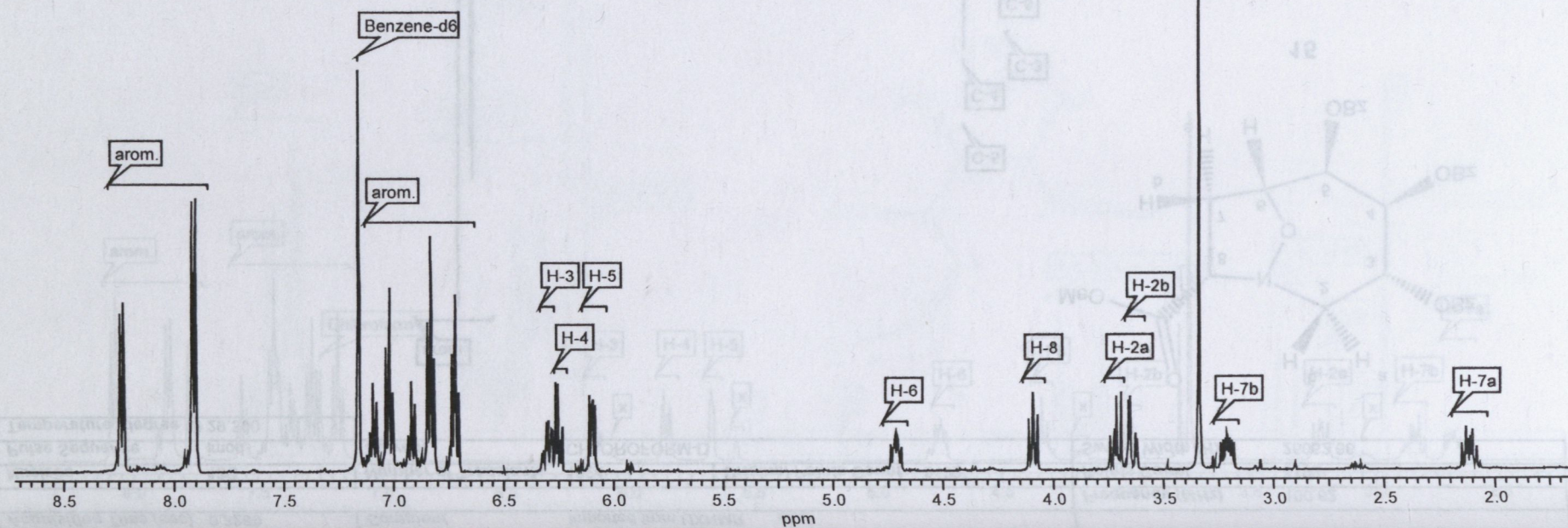




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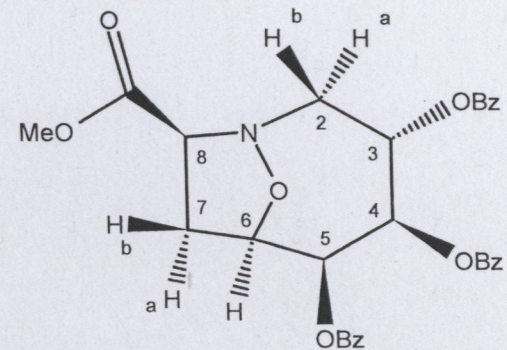
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